Hemodynamic Effects to Inhaled Iloprost in Systemic Sclerosis Associated Pulmonary Arterial Hypertension

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Abstract

Background: Lung is one of the major organ involvements in systemic sclerosis with the manifestation of either pulmonary fibrosis or pulmonary arterial hypertension (PAH). Once PAH is developed, the morbidity and mortality increase significantly. There are few data available regarding the efficacy of inhaled iloprost in patients with systemic sclerosis (SSc) in Thailand.

Objective: To study hemodynamic responsiveness to inhaled Iloprost in patients with systemic sclerosis associated PAH (SScPAH)

Methods: 83 patients with diffused type systemic sclerosis underwent transthoracic echocardiography examination to evaluate right ventricular systolic pressure (RVSP). Right heart catheterization was performed to confirm the diagnosis of PAH in patients who had RVSP more than 35 mmHg.

Results: 22 of 83 patients (26.5%) had SScPAH by echocardiography; 11 patients agreed to have right heart catheterization. PAH was excluded in 3 patients during catheterization, while 8 of 11 were confirmed to have PAH. Mean pulmonary artery pressure (MPAP) was 39.72 ± 9.70 mmHg and mean pulmonary vascular resistance (PVR) was 600.73 ± 265.97 dyne•s•cm⁻⁵. For vasoreactive test responsiveness, 7 of 8 patients (87.5%) were non-responders (reduction of MPAP less than 10 mmHg). However, Reduction of PVR more than 20% was found in 7 of 8 patients, mean %PVR reduction was 37 ± 13%.

Conclusion: PAH is common in patients with systemic sclerosis. The diagnosis of PAH should be confirmed by right heart catheterization. Inhaled Iloprost significantly decreases pulmonary vascular resistance and improves cardiac output in patients with SSc.

Key words: Systemic sclerosis, PAH, vasoreactive response, Iloprost

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease, characterized by diffuse fibrosis of multiple organ systems. The overall incidence of SSc is about 19.1 per million per year (1). There is no definite incidence of SSc reported in Thailand but a high prevalence of SSc patients has been observed in Northeast Thailand (2).

Clinical presentations include classic skin thickening, Raynaud’s phenomenon, gastrointestinal, musculoskeletal, renal, and cardiac involvements such as cardiomyopathy, and pericardial effusion. Among these presentations, systemic sclerosis associated PAH (SScPAH) is one of the leading causes of death in the SSc patient (3). Mukerjee et al (4) showed a declining survival rate after the diagnosis of SScPAH; survival rates were 81%, 63% and 58% at 1, 2, 3 years respectively.

Pulmonary involvement in SSc can be classified by a mechanism into pulmonary fibrosis (PF) or interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). The prevalence of SSc PF was 80% of all SSc patients (5) and of SSc PAH was 18-59.1% (4, 6, 7). Both mechanisms

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result in the same clinical manifestation such as chronic cough, dyspnea on exertion and edema from right sided heart failure. Because SSc associated PF (SScPF) is part of the disease progression and there has yet to be a definitive treatment, although SScPAH has many effective medications, It is crucial to give a definite diagnosis of SScPAH in patients with pulmonary symptoms.

In clinical practice, screening for PAH is done by echocardiography, followed by right heart catheterization for a definite diagnosis and performe an acute vasodilator challenge test during catheterization for defining “responders” (8). Mukerjee et al (4) in 794 SSc patients, found a reduction of prevalence of SScPAH from 18% (diagnosed by echocardiography) to 12% (diagnosed by cardiac catheterization). This finding was similar to the result of Murata et al (9), who showed a reduction of prevalence from 43% to 29%. For Thai SSc patients, there have been very little data regarding this finding.

There are a few studies about the responsiveness to vasodilators in SScPAH . Menon et al (10) performed a vasoreactive test using intravenous prostacyclin in 7 SScPAH patients showing a reduction of pulmonary vascular resistance (PVR) (median 32%). Strange et al (11), using intravenous epoprostenol, found a positive vasoreactive response in 8 of 9 patients. The largest study was done by Mukerjee et al (4). 129 SScPAH patients underwent cardiac catheterization and a vasoreactive test was performed using intravenous Iloprost. He showed a 69% positive vasoreactive response. In Thailand, there is few data available regarding the prevalence of PAH confirmed by right heart catheterization and the efficacy of inhaled Iloprost.

The aims of this study were: 1) to study hemodynamic responsiveness to inhaled Iloprost in Thai systemic sclerosis associated PAH; 2) to evaluate the prevalence of PAH in SSc by right heart catheterization.

Methods
Study population

From July 2008 to January 2009, SSc patients who were being followed by Rheumatologists in the Scleroderma clinic at Srinagarind hospital were actively evaluated and screened for PAH. Cardiac catheterization was performed in all patients who met the following criteria:

1) The right ventricular systolic pressure (RVSP) on transthoracic echocardiography exceeded 35 mmHg.
2) Older than 15 years of age

Patients were excluded with the following conditions:

1) left sided heart failure.
2) hypotension.
3) refused to undergo right heart catheterization.

All patients fulfilled the criteria for the diagnosis of systemic sclerosis by the American College of Rheumatology. Written informed consent was obtained from each patient and the study protocol was approved by the institutional research committee.

Echocardiography

Echocardiographic studies were performed with a 2.5- or 3.5-MHz linear array imaging transducer (Hewlett-Packard Sonos 5500). Color-flow Doppler was used to obtain the tricuspid regurgitation flow and Doppler tricuspid regurgitation velocity was measured by continuous-wave echocardiography. RVSP was measured by continuous wave Doppler echocardiography using the modified Bernoulli equation (RVSP = p2 + right atrial pressure). The right atrial pressure was assumed to be 5 to 10 mmHg, depending on inferior vena cava size and its respiratory variation. Apical four chambers and short axis view were obtained to record optimal tricuspid flow signals. PAH was diagnosed if the Doppler-echocardiography estimated RVSP exceed 35 mmHg.

Cardiac catheterization

Right heart catheterization was performed by the Seldinger technique from the right femoral vein approach using a 7 French Swan-Ganz catheter under local anesthesia. All following hemodynamic parameters were recorded: central venous pressure, right atrial pressure, right ventricular pressure, pulmonary artery systolic and diastolic pressure (PASP and PADP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR). Cardiac output (CO) was measured by using the thermodilution method.

PAH was defined by MPAP exceeding 25 mmHg at rest or 30 mmHg with exercise, and PCWP less than 15 mmHg (7, 12). Patients who met the criteria for PAH underwent a vasoreactive test using 20 ug of inhaled Iloprost. All hemodynamic parameters were reevaluated.
at 30 minutes after inhalation. A positive vasoreactive response or “responder” was defined when MPAP was decreased > 10 mmHg and reached an absolute value of MPAP ≤ 40 mmHg, accompanied by normal or higher cardiac output (13).

**Statistical analysis**

The continuous variables are presented as mean ± SD, and categorical variables are described with frequency and percentages. The differences of all comparisons for the hemodynamic parameters before and after the vasoreactive test was assessed by a paired t test. A p value < 0.05 was considered statistically significant. All the analysis were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA).

**Results**

From July 2008 to January 2009, 83 patients with systemic sclerosis were actively screened for PAH by echocardiography. 22 of 83 patients (26.5%) were diagnosed SScPAH and 11 patients agreed to perform

**Table 1.** Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>number (%) or mean (SD)</th>
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<tbody>
<tr>
<td>Diffused type SSC</td>
<td>8/8 (100%)</td>
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<tr>
<td>Mean age (yr)</td>
<td>53 (35-69)</td>
</tr>
<tr>
<td>Female</td>
<td>6/8 (75%)</td>
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<tr>
<td>NYHA class:</td>
<td></td>
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<tr>
<td>Class II</td>
<td>5 (62.5%)</td>
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<tr>
<td>Class III</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.15 (0.5-4.0)</td>
</tr>
<tr>
<td>Hematocrit (vol %)</td>
<td>35 (27-45)</td>
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<tr>
<td>Albumin (mg/dl)</td>
<td>3.9 (3.4-4.5)</td>
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<tr>
<td>Creatinine kinase (mg/dl)</td>
<td>103 (35-220)</td>
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<tr>
<td>FEV1/FVC</td>
<td></td>
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<tr>
<td>≥ 70</td>
<td>4/4 (100%)</td>
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<tr>
<td>&lt; 70</td>
<td>0</td>
</tr>
<tr>
<td>Present of pulmonary fibrosis (by CXR/HRCT)</td>
<td>8/8 (100%)</td>
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<tr>
<td>ECG findings:</td>
<td></td>
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<tr>
<td>Right atrial enlargement</td>
<td>1/8 (12.5%)</td>
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<tr>
<td>Right ventricular enlargement</td>
<td>3/8 (37.5%)</td>
</tr>
<tr>
<td>Left ventricular enlargement</td>
<td>1/8 (12.5%)</td>
</tr>
<tr>
<td>Echocardiographic findings:</td>
<td></td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>62 (45-77.5)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>70 (52-89)</td>
</tr>
<tr>
<td>RV MPI</td>
<td>0.5 (0.13-0.82)</td>
</tr>
<tr>
<td>LV MPI</td>
<td>0.55 (0.35-0.86)</td>
</tr>
<tr>
<td>Presence of pericardial effusion</td>
<td>3/8 (37.5%)</td>
</tr>
</tbody>
</table>

RVSP, right ventricular systolic pressure; LVEF, left ventricular ejection fraction; RV/LV MPI, right /left ventricular myocardial performance index; FEV1, forced expiratory volume at 1 sec; FVC, forced vital capacity
right heart catheterization. During catheterization, 3 patients did not meet the criteria for PAH, and 8 of 11 patients were included in the study. All patients had diffuse type SSc with symptoms of dyspnea on exertion. The study population mean age was 53 years old. NYHA class IV was found in 2 patients. Evidence of pulmonary fibrosis were found in all patients, either by chest X-ray or high resolution CT. Pulmonary function tests were done in 4 of 8 patients. Baseline characteristics are shown in Table 1.

RVSP values, assessed by echocardiography, of the 3 excluded-patients were 38, 39, and 39 mmHg. In contrast patients with cardiac catheterization confirmed PAH RVSP, assessed by echocardiography was \( \geq 45 \) mmHg (mean RVSP 62 \( \pm \) 12.54 mmHg). We also found 3 of 8 patients (37.5%) with pericardial effusion.

All 8 patients that had right heart catheterization and an acute vasodilator challenge test were without any complications. Mean MPAP was 39.12 \( \pm \) 9.70 mmHg, mean PCWP was 10.75 \( \pm \) 2.81 mmHg, mean PVR was 600.73 \( \pm \) 265.97 dyne•s•cm\(^{-5}\), and mean CO was 4.86 \( \pm \) 2.57 l/min. Hemodynamic parameters before and after inhalation of Iloprost are shown in Figures 1-3.

Pre and post iloprost inhalation hemodynamic data are shown in Table 2. Comparison of hemodynamic parameters before and after an acute vasodilator challenge test showed a significant reduction of RVSP (mean \( 7 \pm 5 \) mmHg, \( p = 0.006 \)), MPAP (mean \( 5.37 \pm 2.5 \) mmHg, \( p = 0.001 \)), and PVR (mean 237.75 \( \pm \) 169.58 dyne\(^{-5}\)•s•cm\(^{-5}\), \( p = 0.005 \)), while CO was significantly increased (mean \( 0.82 \pm 0.96 \) l/min, \( p = 0.045 \)).

For responsiveness to inhaled Iloprost, only 1 of 8 patients had a positive vasoreactive response, while 7 of 8 patients (87.5%) were non-responders, less than 10 mmHg absolute reduction of MPAP. Although only 1 of 8 patients had a decrease of MPAP > 10 mmHg, a marked reduction of PVR was observed in almost every patient. Using a cutoff point of 20% PVR reduction, 7 of 8 patients (87.5%) had more than a 20% PVR reduction (mean %PVR reduction = 37% \( \pm \) 13.48%).

Discussion

This is the first study in Thailand to show hemodynamic data from right heart catheterization and responsiveness to a vasodilator in patients with systemic

Figure 1. PVR (dyne•s•cm\(^{-5}\)) pre and post vasodilator challenge test

![Figure 1](image)

Figure 2. MPAP (mmHg) pre and post vasodilator challenge test

![Figure 2](image)

Figure 3. CO (l/min) pre and post vasodilator challenge test

![Figure 3](image)
sclerosis associated PAH. Prevalence of SScPAH in our study was 26.5%, relatively lower than previous studies reported by Kiatchoosakul et al. (6) and Supaporn et al. (7). The prevalence reported by those studies was 36% and 59.1% respectively. This may be due to an active screening for PAH by echocardiography in both symptomatic and asymptomatic patients in our study.

In the present study, we found that by using a RVSP cutoff ≥ 36 mmHg to define pulmonary hypertension, resulted in an misdiagnosis in 3 of 11 patients. This finding was similar to a previous larger study by Mukerjee et al. (4) which showed a reduction of prevalence of SScPAH from 16% to 12% after cardiac catheterization.

Mukerjee et al (14), in another study, also reported a better sensitivity, specificity and positive predictive value of tricuspid gradient (TG) or RVSP at various thresholds. The sensitivity, specificity and positive predictive value of TG ≥ 35 mmHg were 75%, 66%, and 85% respectively, while higher threshold (TG ≥ 45 mmHg) were 47%, 97%, and 98% respectively. However, in our study, not all patients who were diagnosed with PAH by echocardiography agreed to do cardiac catheterization; in fact, only 11 of 22 patients agreed. We, therefore, could not report the prevalence of SScPAH by cardiac catheterization as well as the sensitivity and specificity of a TG threshold ≥ 36 mmHg for a PAH diagnosis. Although right heart catheterization is an invasive procedure its complication is less than 1% (8). Because of the high treatment cost and the question in accuracy of echocardiography for the diagnosis of PAH, we suggest performing right heart catheterization in order to confirm pulmonary hypertension before initiation of therapy and to evaluate severity of the disease in every patient with SScPAH.

Few studies about the hemodynamic responsiveness to a vasodilator during cardiac catheterization in SScPAH are reported. Menon et al (10) reported the reduction of pulmonary vascular resistance (PVR) in 7 patients (median 32%), Strange et al (11) found a positive vasoreactive responses in 8 of 9 patients, and Mukerjee et al (4) who studied 129 patients, reported a 69% positive vasoreactive response. From previous studies by Menon (10) and Mukerjee (4), the definition of “responders” or positive vasoreactive response was the conventional definition of Rich et al (15) which “responders” were defined as patients with a PVR reduction of > 20 %. By using the same definition, this study also showed 7 of 8 patients with a positive vasoreactive response and the mean % PVR reduction was 37 ± 13%. However, the percentage fall in PVR (“PVR) did not predict survival in previous SScPAH reported by Mukerjee et al. (4)

<table>
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<tr>
<th></th>
<th>Pre mean</th>
<th>Post mean</th>
<th>P value</th>
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<tr>
<td>SBP (mmHg)</td>
<td>145.75 ± 28.36</td>
<td>142.62 ± 30.71</td>
<td>0.580</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7.87 ± 3.44</td>
<td>7.50 ± 3.66</td>
<td>0.549</td>
</tr>
<tr>
<td>RVSP (mmHg)</td>
<td>63.37 ± 17.12</td>
<td>56.37 ± 15.94</td>
<td>0.006</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>39.72 ± 9.70</td>
<td>33.75 ± 8.92</td>
<td>0.001</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>10.75 ± 2.81</td>
<td>12.00 ± 2.82</td>
<td>0.038</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.86 ± 2.57</td>
<td>5.69 ± 3.38</td>
<td>0.045</td>
</tr>
<tr>
<td>PVR (dyne•s•cm⁻²)</td>
<td>600.73 ± 265.97</td>
<td>362.97 ± 183.05</td>
<td>0.005</td>
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</table>

SBP, systolic blood pressure; RAP, right atrial pressure; RVSP, right ventricular systolic pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance
According to ESC guidelines (8), “responders” or positive vasoreactive response is defined by the reduction of absolute MPAP > 10 mmHg and to reach an absolute value of MPAP ≤ 40 mmHg. Although, in the present study, significant reductions of MPAP and PVR values were demonstrated (p = 0.001 and p = 0.005 respectively), there were 7 of 8 patients that had negative vasoreactive responses or were defined as “non-responders”. In clinical practice, the result of a vasoreactive test is used as guidance for management in patients with idiopathic pulmonary hypertension (IPAH). Patients who are defined as a “responder” will be initially treated with calcium channel blockers (CCB). However, less than 10% of IPAH patients are sustained responders and long term treatment with CCB in patients with PAH associated with connective tissue disease (CTD) such as systemic sclerosis is still unclear (15). Furthermore a majority of patients with SSc have usually taken CCB for treatment of Raynaud’s phenomenon and most tend to be intolerant of this medication (16). Acute vasodilator challenge test may not be necessary during right heart catheterization in systemic sclerosis associated PAH.

Limitations

Because the sample size was small, the report in this study may not represent the whole Thai SScPAH population. Therefore a larger sample size is required. Pulmonary function tests and DLCO were not available in all cases; therefore restrictive pulmonary disease could not be completely excluded.

Conclusions

Pulmonary artery hypertension is common in patients with systemic sclerosis. Echocardiography is a useful screening tool; however, right heart catheterization is essential to confirm the diagnosis. Inhaled Iloprost has a favorable effect on pulmonary circulation and cardiac output.

Conflict of Interest

None

References

การตอบสนองของหลอดเลือดแดงปอดต่อกัยโลพลอสในผู้ป่วยโรคหนังแข็ง (Systemic sclerosis) ที่มีความดันหลอดเลือดแดงปอดสูง (PAH)

ดูจดาว สาหัสภรณ์, อรรจนี มหาราภูชา, ทรงศักดิ์เกียรติชูสกุล

บทคัดย่อ
ความดันหลอดเลือดแดงปอดสูงเป็นภาวะแทรกซ้อนในผู้ป่วยโรคหนังแข็ง มีผลให้ถูกระดับการรับเลือดขวีฟั้มที่ช้าน และคุณภาพชีวิตของผู้ป่วยถูกจำกัด ข้อมูลการรักษาด้วยยาโลพลอสถันนิทนั้นไม่ครบถ้วน มีความจำเป็นต้องมีการวิจัยเพิ่มเติมในทางที่จะมีการรักษาด้วยยาโลพลอสที่มีความดันหลอดเลือดแดงปอดสูง

วัตถุประสงค์: เพื่อศึกษาการตอบสนองของหลอดเลือดแดงปอดต่อกัยโลพลอสชนิดพื้นในผู้ป่วยโรคหนังแข็งที่มีความดันหลอดเลือดแดงปอดสูง

วิธีการศึกษา: ทำการตรวจดังกล่าวในผู้ป่วยโรคหนังแข็งโดยใช้คลื่นเสียงสะท้อนหัวใจชนิดความถี่สูงผ่านทางผนังหัวใจและตรวจยืนยันด้วยการตรวจหัวใจห้องขวา ทำการการตอบสนองของหลอดเลือดแดงปอดต่อกัยโลพลอสชนิดพื้น

ผลการศึกษา: ทำการตรวจดังกล่าวในผู้ป่วยจำนวน 83 ราย พบความดันหลอดเลือดแดงปอดสูง 22 รายคิดเป็นร้อยละ 26.5 ผู้ป่วย 11 ราย ได้รับการตรวจดังกล่าวด้วยการการตรวจหัวใจห้องขวา พบผู้ป่วย 3 ราย ไม่มีความดันหลอดเลือดแดงปอดสูง ผู้ป่วย 8 ราย ได้รับการทดสอบด้วยยาโลพลอสชนิดพื้น ผู้ป่วย 7 ใน 8 รายคิดเป็นร้อยละ 87.5 ความดันหลอดเลือดแดงปอดเลือดลดจาก 39.72 ± 9.70 มม.ปรอท เป็น 33.75 ± 8.92 มม.ปรอท ความต้านทานในหลอดเลือดลดจาก 600.73 ± 265.97 dyne•s•cm⁻⁵ เป็น 362.97 ± 183.05 dyne•s•cm⁻⁵ และ Cardiac output เพิ่มจาก 4.86 ± 2.57 L/min เป็น 5.69 ± 3.35 L/min

สรุป: ความดันหลอดเลือดแดงปอดสูงพบได้ในผู้ป่วยโรคหนังแข็ง มีความจำเป็นต้องมีการวิจัยเพิ่มเติมในการรักษาด้วยยาโลพลอสชนิดพื้น เพื่อให้การรักษาด้านเวชภูมิที่ที่จะตอบสนองในหลอดเลือดแดงปอดสูงมีการทำงานทางเส้นท่อหลอดเลือดบวก