D-Dimer and Pulmonary Arterial Hypertension in Systemic Sclerosis

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Background: *Micro-vascular thrombus is a common pathological finding in pulmonary artery hypertension. The association between plasma D-dimer, a marker of thrombus formation, and pulmonary artery hypertension (PAH) in patients with systemic sclerosis is unknown.*
Objective: *To assess the correlation of the level of plasma D-dimer and pulmonary artery pressure in patients with systemic sclerosis.*
Material and Method: *One hundred and twenty nine patients with systemic sclerosis between 19 and 75 years of age (mean, 48 $\pm$ 11.3) entered the study. Plasma D-dimer was determined using immunoturbidimetric assay (D-dimer plus, Dade Behring Inc., Newark, USA). Pulmonary artery pressure was estimated by Doppler echocardiography. PAH was considered present if the Doppler echocardiography-estimated right ventricular systolic pressure (RVSP) exceeded 36 mmHg.*
Results: *Forty-seven patients (36.4%) had PAH according to Doppler echocardiography including 32 (68.1%) mild (RVSP, 36-45 mmHg), nine (19.1%) moderate (RVSP, 46-55 mmHg), and six (12.8%) severe PAH (RVSP $\geq$ 56 mmHg). No significant correlation was found between plasma D-dimer and RVSP ($r = 0.02$, $p = 0.82$).*
Conclusion: *The present study demonstrated that the D-dimmer level is not associated with the level of pulmonary artery pressure in patients with systemic sclerosis, indicating that microvascular thrombosis may not play a significant role in the pathogenesis of PAH in patients with systemic sclerosis.*

Keywords: *D-dimer, Pulmonary hypertension, Systemic sclerosis*

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Pulmonary artery hypertension (PAH) is the cause of considerable morbidity and mortality in patients with systemic sclerosis (SSc). The prevalence of PAH in patients with SSc ranges from 8-16%[1]. PAH impairs the quality of life (QoL) and is one of the leading causes of mortality in SSc patients[2,3]. PAH in association with SSc (PAH-SSc) has an even worse prognosis than idiopathic PAH (IPAH)[4]; if left untreated, the median survival of patients with IPAH is 2.8 years[5,6], whereas it is ~1 year for those with PAH-SSc[2,4].

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The combination of vasoconstriction, vascular-wall remodeling and *in situ* thrombosis lead to an increase in vascular resistance in patients with IPAH[7,8]. Fuster *et al* found that *in situ* thrombosis was a prominent finding in lung vessels from patients with IPAH[9]. Wagenvoort *et al* demonstrated that thrombotic lesions might complicate various types of pulmonary hypertension[10]. While Welsh *et al* found that coagulation activity correlated with high mean pulmonary arterial pressure in patients with severe PAH[11]. These findings suggest that microvascular thrombosis may play a significant role in IPAH.

An early event in the pathogenesis of SSc is vascular dysfunction[12]. Excessive vascoconstriction is followed by structural changes, including

proliferation of intimal, endothelial and smooth muscle cells, and the production of contracted extracellular matrix by activated fibroblasts, resulting in arteriolar occlusion. Although thrombotic vasculopathy can be the cause of PAH in SLE and be associated with antiphospholipid antibodies[13], this has never been documented in PAH-SSc.

Plasma D-dimer, a specific derivative of crossed-linked fibrin, has been comprehensively evaluated as a diagnostic test for disseminated intravascular coagulation and deep vein thrombosis[14-16]. Therefore, the authors hypothesized that the level of D-dimer may be used as a biomarker for indicating the severity of PAH in patients with SSc and may be helpful in identifying SSc patients at risk of PAH.

Material and Method

Patients

This prospective study was conducted between May 2005 and July 2006 at Srinagarind Hospital, Khon Kaen University, Thailand. Consecutive patients fulfilling the American College of Rheumatology (ACR) criteria for the diagnosis of systemic sclerosis[17] were enrolled.

The clinical features recorded at initial presentation to the Scleroderma Clinic included: age, sex, duration of disease, modified Rodnan skin score, functional capacity according to the New York Heart Association (NYHA) classification and the disease subtype (*i.e.*, limited and/or diffuse disease).

Pulmonary fibrosis was determined by high resolution CT scan or abnormal chest X-ray. Patients were excluded if they had any evidence of the following: deep vein thrombosis, infection, acute myocardial infarction, or malignancy.

Written informed consent was obtained from each patient, and the research protocol was approved by the authors' institutional ethics committee.

Echocardiography

Echocardiographic studies were performed with a 2.5- or 3.5-MHz linear array imaging transducer (Hewlett-Packard Sonos 5500). Particular attention was accorded to the identification and quantification of tricuspid regurgitation. Color-flow Doppler was used to obtain the best possible alignment of the tricuspid regurgitation flow and Doppler tricuspid regurgitant velocity was measured by continuous-wave echocardiography.

Right ventricular systolic pressure (RVSP) was measured by continuous wave Doppler echocardiography using the modified Bernoulli equation ($p = 4 v^2 +$ right atrial pressure). The right atrial pressure was assumed to be 10 mmHg. Apical four-chamber and short axis view were obtained to record optimal tricuspid flow signals. PAH was considered present if the Doppler echocardiography-estimated RVSP exceeded 36 mmHg[18]. The severity of PAH was classified as mild (36 to 45 mmHg), moderate (46 to 55 mmHg) or severe ($\geq$ 56 mmHg)[19].

Sample collection and analysis

After obtaining informed consent, 5 mL of blood was collected into vacuum tubes, containing 3.2% sodium citrate. Samples were gently mixed and centrifuged at 3,000 revolutions per minute for 10 minutes. Plasma D-dimer was assayed as recommended by the kit manufacturer using the commercial kit and assay (D- dimer Plus, Dade Behring Inc., Newark, USA).

Statistical analysis

The continuous variables are presented here as means $\pm$ SD, and categorical variables are described with frequencies and percentages. The respective continuous and categorical variables were compared using the *t* and χ^2 test, as appropriate. The correlation between RVSP and the d-dimer level was assessed using Pearson's correlation coefficient (r). A *p*-value of < 0.05 was considered statistically significant. All the analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, Illinois, USA).

Results

One hundred and fifty five patients with systemic sclerosis were enrolled in the present study, of which 26 were excluded: 18 (11.6%) because of having a poor tricuspid velocity signal and eight who did not complete the study protocols. Therefore, 129 patients satisfied the study protocols and were retained for analysis. Table 1 summarizes the clinical characteristics of the studied population. The study population (72.9% female) averaged 48 years of age and 77.3% had diffuse SSc, 69% Raynaud's phenomenon and 73.6% evidence of pulmonary fibrosis either from high resolution CT scan or chest X-ray. The majority of patients (76.7%) had a limited type of SSc and whose mean Rodnan's skin score was 14.4 $\pm$ 7.7.

The respective mean disease duration (months) and age at disease onset was 46.5 $\pm$ 39.3 months and 44.5 $\pm$ 12.6 years. Three-quarters of the patients had an NYHA class of II to III and only one patient had an NYHA class of IV (Table 1).

Table 1. Demographic, clinical characteristics among the 129 systemic sclerosis patients

Characteristic	Mean ± SD or n (%)
Age (years)	48.8 ± 11.3
Female	94 (72.9%)
Age of onset (years)	44.5 ± 12.6
Disease duration (months)	46.5 ± 39.3
Hypertension	8 (6.2)
Smoking	7 (5.4)
Clinical subset	
Diffuse type	99 (76.7)
Limited type	30 (23.3)
Clinical signs and symptoms	
Raynaud's phenomenon	90 (69.8)
Telangiectasia	32 (24.8)
Joint involvement	57 (44.2)
Dysphagia	57 (44.2)
Pulmonary fibrosis	95 (73.6)
Joint deformity	57 (44.2)
Calcinosis cutis	2 (1.6)
Salt pepper appearance	72 (55.8)
Leg edema	6 (4.7)
Modified Rodnan skin score	14.4 ± 7.7
NYHA class	
Class I	28 (21.7)
Class II	81 (62.8)
Class III	19 (14.7)
Class IV	1 (0.8)
RVSP (mmHg)	35.2 ± 11.4

The clinical characteristics and echocardiographic findings of patients with and without PAH are presented in Table 2. The clinical characteristics, including pulmonary involvement and scleroderma subtype, did not differ between the two groups. Overall, 47 patients (36.4%) had PAH by Doppler echocardiography including 32 (68.1%) mild, nine (19.1) moderate and six (12.8%) severe. Among these, 28 (59.6%) had evidence of left ventricular diastolic dysfunction (E/A ratio < 1) and eight (17%) had a left ventricular ejection fraction < 50%. The right ventricular dimensions in patients with PAH compared with those without PAH were larger on echocardiography (2.7 ± 0.4 *vs.* 2.3 ± 0.4 mm, p = 0.00). There was no significant correlation between D-dimer and RVSP (r = 0.02, p = 0.82) (Fig. 1).

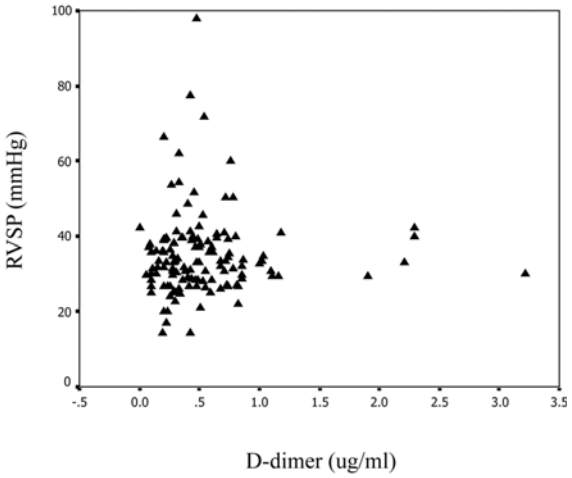

Fig. 1 Correlation between right ventricular systolic pressure (RVSP) and plasma D-dimer (r = 0.02, p = 0.82)

Discussion

The present study demonstrates that the level of plasma D-dimer is not associated with severity

Table 2. Clinical characteristics, echocardiographic findings and D-dimer level in patients with and without pulmonary artery hypertension (PAH)

Parameter	No PAH (n = 82)	PAH (n = 47)	p-value
Age (years)	47.5 ± 11.6	50.9 ± 0.5	0.54
Age of onset (years)	42.9 ± 12.3	47.2 ± 12.7	0.74
Disease duration (months)	47.4 ± 40.9	44.8 ± 36.6	0.69
Limited systemic sclerosis	25.9%	17.0%	0.34
Pulmonary fibrosis	70%	78.7%	0.43
Raynaud's phenomenon	70.4%	70.2%	0.98
Rodnan skin score	13.9 ± 7.5	15.28.1	0.35
RV diameter	2.3 ± 0.4	2.70.4	0.00
LVEF (%)	61.4 ± 8.6	61.6 ± 10.5	0.94
LV mass index (g/m^2)	100.4 ± 31.8	95.2 ± 28.5	0.36

of PAH and may not be helpful in screening patients with SSc at risk of PAH.

One third of patients with SSc in the present study had PAH detected by Doppler echocardiography. The development of PAH between patients with limited type SSc and those with diffuse type of SSc was not different in the present study. The authors also found that age of onset and duration of disease had no influence on the occurrence of PAH.

PAH has been observed in all connective tissue diseases; however, it occurs most frequently in SSc and is the leading cause of death in such patients[20]. Histopathological changes in PAH associated with SSc are in general indistinguishable from those of idiopathic pulmonary artery hypertension. In patients with primary pulmonary hypertension, previous studies suggested that thrombosis was important in the pathogenesis of pulmonary hypertension[9,21]. Several studies also showed a correlation between laboratory markers and the severity of primary pulmonary hypertension[22,23]. Shitrit *et al* demonstrated in a small study (n = 14) that high D-dimer levels were associated with the severity of pulmonary artery pressure in patients with IPAH[24].

Previous studies agreed that vasculopathy is a pivotal feature of PAH-SSc as the release of endothelin from endothelial cell injury leads to severe vasoconstriction[25]. Moreover, endothelin has been shown to cause vascular hypertrophy, inflammation[25,26], and to have mitogenic effects on fibroblasts. It also stimulates collagen synthesis by fibroblasts and inhibits the production of collagenase, thus contributing to fibrosis[27]. In systemic sclerosis, the pathogenesis of vascular lesions and fibrosis are thought to impair endothelial function, as suggested by impairment of fibrinolysis and activation of the coagulation pathway. Some earlier investigations suggested that systemic sclerosis patients might be characterized by a procoagulant state, reporting depressed basal and stimulated fibrinolytic activity, while other studies have reported normal plasma fibrinolytic activity and normal plasma tissue plasminogen activator[28,29]. Notwithstanding, Lippi *et al* found no correlation between the plasma D-dimer concentration and age, sex and pulmonary involvement[30]; but, none of these studies tested the correlation between D-dimer and the severity of PAH in patients with systemic sclerosis.

D-dimer is a screening test for systemic prothrombotic state[31,32] and could be reliably used as an initial test in patients with clinically-suspected thrombosis. Plasma concentration of D-dimer is sensitive for the presence of thrombotic complications in various diseases (*e.g.*, deep vein thrombosis and pulmonary embolism)[33,34]. The thrombotic tendency of systemic sclerosis and PAH is not well understood. The present study demonstrates that the level of D-dimmer is not associated with the level of pulmonary artery pressure in patients with systemic sclerosis indicating that microvascular thrombosis may not play a significant role in the pathogenesis of PAH in patients with SSc. To the best of the authors' knowledge, this is the first study to test the significance of plasma D-dimer in patients with systemic sclerosis with PAH.

Limitations

There are several limitations in the present study. Firstly; right heart catheterization, the gold standard for the diagnosis of pulmonary hypertension, was not performed; however, it is invasive, whereas Doppler echocardiography, which the authors used, is non-invasive and its derived estimates of pulmonary artery systolic pressure are similar to the gold standard[35]. Secondly, tricuspid regurgitant velocity could be not obtained in all of the presented patients, making it impossible to estimate pulmonary artery systolic pressure. Finally, other significant variables associated with pulmonary artery hypertension in systemic sclerosis (*e.g.*, autoantibodies, anticentromere antibody) and the diffusion capacity of the lung for carbon monoxide (DLCO) were not available.

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ความสัมพันธ์ระหว่างระดับดีไดเมอร์และความดันหลอดเลือดแดงปอดในผู้ป่วยโรคหนังแข็ง

ทรงศักดิ์ เกียรติซูสกุล, วิชัย อังคเศกวินัย, ไชยสิทธิ์ วงศ์วิภาพร, ปิยทัศน์ ทัศนาวิวัฒน์, ชิงชิง ฟู่เจริญ, ศิรภพ สุวรรณโรจน์, รัตนวดี ณ นคร

ภูมิหลัง*: ความดันหลอดเลือดแดงปอดสูงเป็นภาวะแทรกซ้อนที่พบได้บ่อยในผู้ป่วยโรคหนังแข็งทั่วร่าง ภาวะลิ่มเลือดอุดหลอดเลือดแดงปอดเป็นพยาธิสภาพที่สำคัญในผู้ป่วยที่มีความดันในหลอดเลือดแดงปอดสูงที่ไม่ทราบสาเหตุ อย่างไรก็ตามความสัมพันธ์ระหว่างระดับดีไดเมอร์ ซึ่งเป็นตัวแสดงถึงการเกิดลิ่มเลือดในหลอดเลือด และความดันหลอดเลือดแดงปอดในผู้ป่วยโรคหนังแข็งยังไม่เป็นที่ทราบแน่ชัด*

วัตถุประสงค์*: เพื่อศึกษาหาความสัมพันธ์ระหว่างระดับดีไดเมอร์ และความดันหลอดเลือดแดงปอดในผู้ป่วยโรคหนังแข็ง*

วิธีการศึกษา*: ศึกษาผู้ป่วยโรคหนังแข็งจำนวน 129 ราย อายุ 19-75 ปี (เฉลี่ย 48 ปี) โดยตรวจวัดระดับดีไดเมอร์ในเลือดด้วยวิธี immunoturbidimetric และวัดระดับความดันหลอดเลือดแดงปอดโดยการตรวจคลื่นเสียงสะท้อนหัวใจผ่านทางผนังทรวงอก ผู้ป่วยที่มีค่า right ventricular systolic pressure มากกว่า 36 มม.ปรอท ถือว่ามีความดันในหลอดเลือดแดงปอดสูง*

ผลการศึกษา*: การศึกษานี้พบว่าในผู้ป่วยโรคหนังแข็ง 129 ราย มีภาวะความดันหลอดเลือดแดงปอดสูงร้อยละ 36.4 โดยส่วนใหญ่เป็นชนิดที่ไม่รุนแรง และพบว่าระดับดีไดเมอร์ในเลือด ไม่มีความสัมพันธ์กับระดับความดันหลอดเลือดแดงปอด*

สรุป*: ระดับดีไดเมอร์ในเลือดของผู้ป่วยโรคหนังแข็ง ไม่มีความสัมพันธ์กับระดับความดันหลอดเลือดแดงปอดซึ่งอาจจะเป็นตัวบ่งชี้ว่า การเกิดลิ่มเลือดในหลอดเลือดแดงปอดอาจจะไม่ใช่พยาธิสภาพที่สำคัญของการเกิดความดันหลอดเลือดแดงปอดสูงในผู้ป่วยโรคหนังแข็ง*