Primary Pulmonary Hypertension Is Not Associated With Scleroderma-Like Changes in Nailfold Capillaries*

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**Study objectives:** To determine whether primary pulmonary hypertension (PPH) is associated with scleroderma-like changes in nailfold capillaries.

**Design:** Blinded, prospective, case-control study.

**Setting:** University medical centers in Baltimore, MD.

**Patients:** Thirty-seven patients with PPH, 15 patients with scleroderma, and 13 healthy control subjects.

**Measurements:** Subjects underwent nailfold capillary videomicroscopy of the fourth digits of both hands. Capillary images were evaluated by two blinded, trained graders according to standardized criteria for the presence of scleroderma nailfold changes.

**Results:** The prevalence of scleroderma-associated nailfold changes in patients with PPH (1 of 37 patients) was dramatically lower than that in patients with scleroderma (9 of 15 patients; p < 0.0001). The distribution of nailfold grades for the PPH patients was indistinguishable from that of the healthy control subjects.

**Conclusion:** PPH is not associated with scleroderma-like vasculopathy of nailfold capillaries.

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**Key words:** primary pulmonary hypertension; scleroderma; nailfold capillaroscopy

**Abbreviations:** PPH = primary pulmonary hypertension

Primary pulmonary hypertension (PPH) is a frequently fatal condition, the causes of which remain uncertain.1 Mutations of the BMPR-II gene have been associated with the familial form of the disease but have been found in only a minority of sporadic cases.2 Pulmonary hypertension is also a leading cause of mortality and morbidity in patients with systemic sclerosis (scleroderma).3,4 Histologic studies of the lung lesions in patients with PPH demonstrate a diffuse vasculopathy that is similar to that seen in those with scleroderma.5,6 Some patients who have received diagnoses of PPH have other features that overlap with scleroderma, such as Raynaud’s phenomenon and antinuclear antibodies.7 Moreover, prostaglandin therapy has proved to be effective both for PPH and for scleroderma-associated pulmonary hypertension.8,9 Given the similarities between PPH and scleroderma, the possibility has been raised that cases of PPH represent a forme fruste of scleroderma.10 Therefore, we investigated whether PPH also was associated with a form of extrapulmonary vascular disease that is prominent in patients with scleroderma.

Examination of the nailfold capillaries has been made popular as a means of evaluating small blood vessels in the peripheral circulation in humans.11 Scleroderma-specific nailfold capillary abnormalities have been identified and have been found to be consistently distinguishable by a blinded observer.12 The classic changes observed in the scleroderma are nailfold capillary dropout with decreased capillary density and giant nailfold capillaries. The presence of scleroderma-associated nailfold abnormalities has been associated with progression to scleroderma in a cohort of patients presenting with Raynaud’s phe-
To our knowledge, there have been no investigations that examine the nailfold capillaries of PPH patients to determine whether changes comparable to those in patients with scleroderma are found.

This study examined the nailfold capillaries from PPH patients, scleroderma patients, and healthy control subjects. The prevalence of nailfold capillary abnormalities in PPH patients was much lower than that in scleroderma patients and was not significantly different from that in healthy control subjects. Thus, the features of systemic vasculopathy that are seen in scleroderma patients do not develop in PPH patients.

**Materials and Methods**

**Subjects**

A cohort of 37 PPH patients, 8 scleroderma patients with pulmonary hypertension, 8 patients with other forms of secondary pulmonary hypertension, 7 scleroderma patients without pulmonary hypertension, and 13 control subjects was recruited between May and October 1998 at university medical subspecialty clinics in Baltimore, MD. Consecutive patients attending the clinics were recruited until enrollment targets were met. Family history was obtained. No known cases of familial PPH were included in this cohort. Study protocols were approved by the institutional review board committees for the clinics from which the patients were recruited.

**Clinical Data**

Pulmonary hypertension was defined to be present if the mean pulmonary artery pressure was > 25 mm Hg, as determined by right heart catheterization, or the estimated right ventricular systolic pressure was > 35 mm Hg by Doppler cardiac ultrasonography. Patients with pulmonary hypertension were classified as having PPH if they had no other disease process known to be associated with pulmonary hypertension. The American Rheumatism Association criteria were used to confirm the diagnosis of scleroderma. Raynaud's phenomenon was identified using a standardized questionnaire. The epoprostenol infusion history was determined by chart review.

**Nailfold Imaging**

Nailfold capillary videomicroscopy was performed on the fourth fingers of both hands by an operator (E.L.G.) who was blinded to the subjects’ clinical status. Mock infusion pumps were randomly placed on subjects to blind the operator to their epoprostenol treatment status. Imaging was performed after at least 30 min of equilibration in a 24°C temperature-controlled room. Immersion oil was applied to the nailfold before imaging. Recordings were made using a video camera (model KP-160; Hitachi; Brisbane, CA) and a video recorder (S-VHS; Panasonic; Secaucus, NJ) mounted on an stereo zoom microscope (model 52-Tr; Olympus; Melville, NY). Lighting was supplied by a high-intensity fiber-optic light source. A 5-mm measurement standard was applied to the digit and was included in each image.

**Grading and Classification of Nailfold Images**

As part of the prospective design of the study, the nailfold recordings were presented in random order to two blinded, trained graders (F.M.W. and R.A.W.) for classification. The graders both had participated in a previous multicenter trial performing nailfold capillary grading and had been further...
trained using a video atlas to assess for capillary loop enlargement, capillary loop dropout, capillary density, and tortuous or bushy capillaries. The graders summarized their assessment of each digit as bushy capillaries. The graders summarized their assessment of each digit as “scleroderma” (ie, corresponding to Maricq class II or class III changes\textsuperscript{13}), “abnormal but not scleroderma,” or “normal” (Fig 1). Also, the graders assessed the quality of the images as “good” (ie, the number and pattern of all nailfold loops clearly visible over at least a 5-mm span), “fair” (ie, the number of total loops but not the morphology of all loops clearly visible over the best 5-mm span), or “poor” (ie, the number and morphology of loops uncertain over the best 5-mm span). The blinded graders met to resolve all divergences in grading. Nailfold scores on the most abnormal hand were used for analysis. For secondary outcome measures, a single, blinded, trained grader (E.L.G.) evaluated each nailfold image strictly for capillary density and the presence or absence of tortuous or bushy capillaries.

Statistical Analysis

Group means were compared with Student’s t test results. Independent group proportions were compared using Fisher’s Exact Test or the χ² test. Agreement between test conditions was assessed with the κ statistic.\textsuperscript{19} Statistical significance was set at p < 0.05. The Bonferroni correction was used in cases in which multiple comparisons were performed. Results were calculated using computer software (Prism, version 3.0 for Windows; Graphpad Software; San Diego, CA; and SPSS, version 10.0 for Windows; SPSS; Chicago, IL).

RESULTS

Clinical Features of the Cohort

This project recruited 52 patients with pulmonary hypertension, 8 additional patients with scleroderma, and 13 healthy control subjects. Of the 52 subjects with pulmonary hypertension, 37 had PPH, 7 had scleroderma, and 8 had other forms of secondary pulmonary hypertension. Of the eight patients recruited who had received a diagnosis of scleroderma, one also had pulmonary hypertension (trans-thoracic echocardiography was performed in every scleroderma patient who was enrolled except for two who had no clinical signs of pulmonary hypertension and normal diffusing capacity results on pulmonary function testing). Clinical characteristics of the patient groups were compared (Table 1). A trend toward an older mean age in the scleroderma patients compared to the healthy control subjects and PPH patients did not reach significance (p > 0.03). Compared to the healthy control subjects, more of the scleroderma patients were women (p = 0.005). Raynaud’s phenomenon was significantly more common in the scleroderma patients (100%) than in the healthy control subjects (7.7%; p < 0.0001), the PPH patients (8.1%; p < 0.0001), or the patients with nonscleroderma secondary pulmonary hypertension (25.0%; p = 0.0003).

Performance of Video Assessment Protocol

Video images of the fourth fingers of both hands for all 73 subjects (146 images) were presented in random order to two blinded graders. Image-quality assessments were concordant in 87 fingers (59.6%). The graders’ clinical assessments of each nailfold image were concordant in 79 fingers (54.1%), and there were only 5 fingers (3.4%) in which one grader judged the nailfold to be scleroderma while the other grader judged the nailfold to be normal. Overall, fair agreement in clinical assessments existed between the two graders for each digit (κ = 0.29).

To assess the consistency of nailfold capillary changes, the grades for the right hand were compared with the left hand for all 73 study subjects (Table 2). Fair agreement was noted in the assessments of the paired hands for each patient

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy Control Subjects</th>
<th>PPH</th>
<th>SPH</th>
<th>SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>43.0 ± 13.7</td>
<td>45.4 ± 12.5</td>
<td>46.4 ± 15.4</td>
<td>53.6 ± 10.8</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>32</td>
<td>5</td>
<td>151</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>151</td>
</tr>
<tr>
<td>PG12 Rx</td>
<td>NA</td>
<td>21</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>PHTN</td>
<td>NA</td>
<td>37</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD or No. of patients. PPH = secondary pulmonary hypertension excluding scleroderma; SSc = scleroderma; PG12 Rx = treated with epoprostenol infusion; NA = not applicable.

†p = 0.005 vs healthy control subjects (Fisher’s Exact Test).

‡p < 0.0004 vs all other groups (Fisher’s Exact Test).
vessel abnormalities and some clinical features, this study found no evidence that cases of PPH are a forme fruste of scleroderma. Using previously validated criteria for the evaluation of nailfold capillary images and a blinded case-control study design, PPH was not associated with scleroderma-like extrapulmonary vasculopathy in the digital bed. The results of nailfold capillary microscopy of patients with PPH were substantially different from those of scleroderma patients and were indistinguishable from those of healthy control subjects. Only 1 of 37 patients who had received diagnoses of PPH showed scleroderma-like nailfold abnormalities. This patient also had severe Raynaud’s phenomenon.

The proportion of scleroderma patients with classic nailfold changes observed in the current study (9 of 15 patients; 60%) is similar to that in an earlier study20 of videomicroscopy on the fourth digit nailfolds of scleroderma patients in which 43% of patients had classic nailfold changes. The presence in our cohort of one scleroderma patient who both graders agreed had normal capillary morphology on one hand and classic scleroderma changes on the contralateral hand emphasizes that inspection of multiple nailfolds be performed before concluding that scleroderma nailfold changes are absent. In an earlier trial21 of nailfold microscopy, classic nailfold changes were also inconsistent in the fingers of scleroderma patients. Dilated capillaries were present in 42% of digits, markedly decreased capillary density was present in 35%, and avascular areas were present in 26%.

In addition to its immediate vasodilatory effects on the pulmonary vasculature, epoprostenol gradually reduces pulmonary vascular resistance with pro-

### Table 3—Prevalence of Scleroderma-Like Nailfold Changes in PPH Patients*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy Control Subjects† (n = 13)</th>
<th>PPH Patients§ (n = 37)</th>
<th>SSc Patients (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal nailfolds</td>
<td>46.2 (6)</td>
<td>43.2 (16)</td>
<td>6.7 (1)</td>
</tr>
<tr>
<td>Abnl, not SSc nailfolds</td>
<td>53.8 (7)</td>
<td>34.1 (20)</td>
<td>33.3 (5)</td>
</tr>
<tr>
<td>SSc nailfolds</td>
<td>0.0 (0)</td>
<td>2.7 (1)</td>
<td>60.0 (9)</td>
</tr>
</tbody>
</table>

*Values given as % (No. of patients). Values reported are from the most abnormal hand from each subject. See Tables 1 and 2 for abbreviations not used in the text.
†p = 0.002 (χ² test [2 × 3] vs scleroderma patients).
‡p < 0.0001 (χ² test vs scleroderma patients).

(k = 0.37). All analyses were repeated with patients classified by their least abnormal hand, their right hand, or their left hand, and they did not significantly differ from those presented using the most abnormal hand.

**PPH vs Scleroderma Nailfold Comparisons**

The prevalence of nailfold grades was compared between groups using the 2 × 3 χ² test (Table 3). The healthy control subjects and the PPH patients each were clearly different from the scleroderma patients in nailfold grading results (χ² test, p = 0.002 and p < 0.0001, respectively) and were not significantly different from each other. The mean nailfold capillary density was also lower in the scleroderma patients (mean ± SD), 25.9 ± 12.8 loops per 5 mm) than in the healthy control subjects (mean, 36.5 ± 8.7 loops per 5 mm; p = 0.019) or the PPH patients (mean, 41.2 ± 10.7 loops per 5 mm; p < 0.0001). The only PPH patient with nailfolds that graded as scleroderma had a history of recent-onset Raynaud’s phenomenon.

Nailfold grading was not different in scleroderma patients with pulmonary hypertension (normal, 1 of 8 patients; abnormal not scleroderma, 2 of 8 patients; scleroderma, 5 of 8 patients) compared to scleroderma patients without pulmonary hypertension (normal, 0 of 7 patients; abnormal not scleroderma, 3 of 7 patients; scleroderma, 4 of 7 patients). Overall, nailfold grade prevalence also was not affected by epoprostenol treatment status (Table 4). No differences in nailfold capillary density were observed between epoprostenol-treated and untreated subgroups of PPH patients or scleroderma patients (not shown). Bushy or tortuous capillaries tended to be more prevalent in the nailfolds of PPH patients who had been treated with epoprostenol (76.2%) than in those of untreated PPH patients (50.0%; p = 0.027 [Fisher’s Exact Test]). The prevalence of bushy or tortuous capillaries was > 85% in the nailfolds of both treated and untreated scleroderma patients.

### Discussion

While PPH and scleroderma share pulmonary vessel abnormalities and some clinical features, this

### Table 4—Nailfold Classifications With and Without Patients Receiving Epoprostenol Therapy*

<table>
<thead>
<tr>
<th>Variables</th>
<th>SSc + (PGI2)</th>
<th>SSc − (PGI2)</th>
<th>PPH + (PGI2)</th>
<th>PPH − (PGI2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Abnl, not SSc</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* + PGI2 = treated with epoprostenol; − PGI2 = not treated with epoprostenol. See Tables 1 and 2 for abbreviations not used in the text.
longed infusion, presumably due to the remodeling of pulmonary vessels. Our study noted an increased prevalence of tortuous and bushy capillaries after PPH patients had received epoprostenol therapy. Although this difference was not statistically significant, the trend of differences is of interest. Additional studies will be needed to establish whether epoprostenol therapy leads to the remodeling of nailfold capillary vessels. Epoprostenol infusion is known to be an effective treatment for Raynaud’s phenomenon.

This study provides evidence that PPH and scleroderma are distinct entities, even though they lead to similar histologic lesions in the pulmonary vascular bed. The presence of clear-cut scleroderma nailfold changes in a patient with pulmonary hypertension should lead to a high index of suspicion for a scleroderma-spectrum disorder.

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