**Objective:** Pulmonary hypertension with pathological changes similar to those observed in primary pulmonary hypertension occurs in patients with systemic lupus erythematosus (SLE). The efficacy of chronic epoprostenol therapy in SLE has not been well described. The objective of this paper is to describe our experience with long-term epoprostenol therapy in patients with pulmonary hypertension associated with SLE.

**Design:** Case series of six patients with SLE and associated pulmonary hypertension receiving chronic treatment with epoprostenol.

**Results:** All 6 patients had severe pulmonary hypertension. Mean pulmonary artery pressure (mPAP) was 57 ± 9 mm Hg (mean ± SD), and pulmonary vascular resistance was 14 ± 7 units before beginning therapy with epoprostenol. In 4 patients who underwent repeat hemodynamic evaluation (9 to 16 months after starting epoprostenol), mean pulmonary artery pressure decreased by 38 ± 21% and pulmonary vascular resistance by 58 ± 12%. Clinically, all patients improved from New York Heart Association class III or IV to class I or II. Doses of epoprostenol ranged from 4 to 46 ng/kg/min, and the longest duration of therapy has been 2.5 years. Side effects from epoprostenol have not differed from those seen in patients with primary pulmonary hypertension, and except for one patient, there has been no exacerbation of SLE.

**Conclusion:** Epoprostenol was effective for the treatment of pulmonary hypertension in this small group of patients with SLE. Further evaluation of epoprostenol therapy for patients with SLE and other diseases associated with pulmonary hypertension is warranted.

*(CHEST 2000; 117:14–18)*

**Key words:** epoprostenol; pulmonary hypertension; systemic lupus erythematosus

**Abbreviations:** CREST = variant of scleroderma characterized by calcinosis, Raynaud’s phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia; mPAP = mean pulmonary artery pressure; PAP = pulmonary artery pressure; PPH = primary pulmonary hypertension; PVR = pulmonary vascular resistance; SLE = systemic lupus erythematosus

Severe arteriopathy of the pulmonary vascular bed is seen in patients with primary pulmonary hypertension (PPH)¹ and in association with other illnesses such as congenital heart disease,² the scleroderma spectrum of diseases,³–⁵ and, less commonly, systemic lupus erythematosus (SLE).⁶–¹⁰ Treatment of PPH with IV epoprostenol (prostacyclin) has been shown to improve hemodynamics and quality of life and to prolong survival in patients unresponsive to...
conventional therapy. While epoprostenol is not yet approved for secondary causes of pulmonary hypertension, there are reports of significant benefit from its use in patients with scleroderma/CREST syndrome and other connective tissue diseases. Most recently, epoprostenol has been reported to benefit patients with congenital heart disease-associated pulmonary hypertension.

Over the past two and a half years, we treated six patients with SLE and pulmonary hypertension with continuous IV epoprostenol, four of whom underwent repeat hemodynamic evaluation (9 to 16 months after starting epoprostenol). All six patients presented with rapidly progressing symptoms due to pulmonary hypertension. None demonstrated significant improvement with acute vasodilator testing during diagnostic right heart catheterization. We herein describe these six patients in detail, review the treatment of pulmonary hypertension in patients with SLE, and discuss the role of epoprostenol therapy in patients with SLE.

Materials and Methods

We included all patients with the diagnosis of SLE, without evidence of other connective tissue diseases, treated with chronic epoprostenol therapy at our institutions. Patient selection criteria also included: 1) confirmation of the diagnosis of pulmonary hypertension by right heart catheterization; 2) exclusion of other causes of pulmonary hypertension; 3) lack of acute pulmonary vasoreactivity either with inhaled nitric oxide or IV epoprostenol, depending on the protocol used at each institution; and 4) a disease stage of functional class III or IV, as measured by the New York Heart Association.

Results

All patients were women between the ages of 26 and 34, diagnosed with SLE 2 to 19 years before developing pulmonary hypertension. All patients were nonsmokers, without a history of pulmonary emboli or appetite suppressant use. At the time pulmonary hypertension was diagnosed, five patients were receiving prednisone, three were receiving other immunosuppressive medications (azathioprine in two patients and hydroxychloroquine in one patient), four were receiving calcium channel blockers, and one patient was using supplemental oxygen (Table 1). Initial symptoms of pulmonary hypertension were dyspnea on exertion in four patients and syncope in one.

Echocardiograms did not reveal left heart dysfunction or valvular disease in any patient. Pulmonary function testing demonstrated a mild restrictive defect in two patients and a moderate defect in one patient who had no evidence of fibrosis on high resolution CT of the chest. Diffusing capacity was reduced in four patients (Table 1). Antiphospholipid antibodies were present in three patients, one of whom was found to have a deep vein thrombosis of the lower extremity during the initial evaluation for pulmonary hypertension; however, a pulmonary angiogram revealed no evidence of thromboembolic disease. Ventilation-perfusion scans were interpreted as low probability or normal in the other five patients.

All patients underwent diagnostic right heart catheterization with acute vasodilator testing (Table 2). Nitric oxide was used to assess vasoreactivity in two patients, epoprostenol was used in three patients, and both nitric oxide and epoprostenol were used in one patient. No patient demonstrated a decrease in mean pulmonary artery pressure (mPAP) > 13%, although two patients had an increase in cardiac output with acute testing with epoprostenol, leading to a decrease in pulmonary vascular resistance (PVR) > 20%. One of these patients was not started on epoprostenol until 2 months later when her clinical condition worsened; the other was identified as NYHA class IV, with a mean right atrial pressure of 15 mm Hg, and was started on a chronic infusion of epoprostenol at the time of catheterization.

All six patients improved significantly while receiving long-term epoprostenol (>12 weeks of continu-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Medications</th>
<th>PFTs</th>
<th>APLA</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>Prednisone, azathioprine, CCB</td>
<td>TLC, 61%, DLCO, 55%</td>
<td>No</td>
<td>III/VI</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>Prednisone</td>
<td>TLC, 75%</td>
<td>Yes</td>
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</tr>
<tr>
<td>3</td>
<td>26</td>
<td>Prednisone, azathioprine, CCB</td>
<td>DLCO, 73%</td>
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<td>III</td>
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<tr>
<td>4</td>
<td>35</td>
<td>Supplemental oxygen</td>
<td>FEV1, 78%</td>
<td>Yes</td>
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</tr>
<tr>
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<td>TLC, 68%, DLCO, 60%</td>
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<td>III</td>
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<tr>
<td>6</td>
<td>34</td>
<td>Prednisone, CCB</td>
<td>DLCO, 40%</td>
<td>No</td>
<td>IV</td>
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</table>

*CCB = calcium channel blockers; PFTs = pulmonary function tests, presented as % of predicted values; TLC = total lung capacity; DLCO = diffusing capacity for carbon monoxide; FEV1 = forced expiratory volume in one second; APLA = antiphospholipid antibodies; NYHA = New York Heart Association class heart failure.
ous administration and are currently identified as NYHA class I or II. Doses of epoprostenol range from 4 to 46 ng/kg/min, with follow-up from 3 months to 2.5 years. All patients have been treated with oral anticoagulants in addition to epoprostenol. Four patients have undergone repeat right heart catheterization, 9 to 16 months after starting epoprostenol (Table 3). PVR decreased substantially in all patients, with a mean decrease of 62\%\(\pm\)12\%. The two patients who did not undergo repeat right heart catheterization have had repeat echocardiograms 3 months after starting therapy, which demonstrates a decrease in the estimated systolic PAP of 20 mm Hg in one and 35 mm Hg in the other.

Side effects from epoprostenol have been similar to those seen in patients with PPH, including nausea, jaw pain, headache, and diarrhea. One patient with antiphospholipid antibodies developed a right subclavian and jugular vein thrombosis requiring removal of a Hickman catheter. In addition, she developed severe thrombocytopenia. Both of these complications were thought to be associated with a flare of SLE, and both responded to increased immunosuppressive medications and to IV immunoglobulin. The patient has been maintained on oral anticoagulants without further problems.

### Table 2—Baseline Hemodynamics and Response to Acute Vasodilator Testing*

<table>
<thead>
<tr>
<th>Patient</th>
<th>mPAP (mmHg)</th>
<th>mPWP (mmHg)</th>
<th>CO (L/min)</th>
<th>PVR (Units)</th>
<th>Acute Vasodilator</th>
<th>Maximal Dose of Vasodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-</td>
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<td>Pre-</td>
<td>Post-</td>
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<tr>
<td>1</td>
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<td>62</td>
<td>15</td>
<td>20</td>
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<tr>
<td>2</td>
<td>58</td>
<td>60</td>
<td>8</td>
<td>9</td>
<td>3.5</td>
<td>4.1</td>
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<tr>
<td>3</td>
<td>48</td>
<td>52</td>
<td>14</td>
<td>10</td>
<td>3.8</td>
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<tr>
<td>4</td>
<td>61</td>
<td>53</td>
<td>13</td>
<td>11</td>
<td>2.1</td>
<td>4.7</td>
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<tr>
<td>5</td>
<td>45</td>
<td>42</td>
<td>6</td>
<td>7</td>
<td>4.9</td>
<td>5.1</td>
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<tr>
<td>6</td>
<td>70</td>
<td>67</td>
<td>13</td>
<td>13</td>
<td>2.7</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Average \(\pm\) SD: 57 \(\pm\) 9 mPAP; 56 \(\pm\) 9 mPWP; 12 \(\pm\) 4 CO; 12 \(\pm\) 5 PVR; 3.7 \(\pm\) 1.2; 4.7 \(\pm\) 0.4; 14.0 \(\pm\) 6.6; 9.4 \(\pm\) 2.8

*See footnotes in Tables 1 and 2 for abbreviations.

### Table 3—Repeat Hemodynamics During Chronic Infusion of Epoprostenol*

<table>
<thead>
<tr>
<th>Patient</th>
<th>mPAP</th>
<th>mPWP</th>
<th>CO</th>
<th>PVR</th>
<th>Dose†</th>
<th>Time‡</th>
<th>NYHA</th>
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<tbody>
<tr>
<td>Pre-</td>
<td>Post-</td>
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<td></td>
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<tr>
<td>1</td>
<td>28</td>
<td>12</td>
<td>5.6</td>
<td>2.7</td>
<td>21</td>
<td>16</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>13</td>
<td>6.5</td>
<td>6.2</td>
<td>2</td>
<td>9</td>
<td>I/II</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>9</td>
<td>6.3</td>
<td>3.3</td>
<td>46</td>
<td>12</td>
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<tr>
<td>5</td>
<td>21</td>
<td>2</td>
<td>5.2</td>
<td>3.7</td>
<td>17</td>
<td>15</td>
<td>II</td>
</tr>
</tbody>
</table>

Average \(\pm\) SD: 33 \(\pm\) 14 mPAP; 9 \(\pm\) 5 mPWP; 5.9 \(\pm\) 0.6 CO; 4.0 \(\pm\) 1.5 PVR; 22 \(\pm\) 18

### Discussion

Studies of patients with SLE have found a prevalence of pulmonary hypertension ranging from 9 to 14\%\(^7,8,10\) and an overall 2-year mortality \(\geq\) 50\% when pulmonary hypertension is present.\(^18\) Many patients in these reports either had significant restrictive lung disease or the data were inadequate to determine the etiology of the pulmonary hypertension. In addition, PAP elevation was generally modest. There are only a few case reports in the literature of patients with SLE and severe pulmonary hypertension resulting in right heart failure.\(^9,19–22\) Autopsy findings from these patients have demonstrated pathologic changes of medial hypertrophy, intimal fibrosis, and plexiform lesions, which are virtually identical to the alterations seen in patients with PPH. Consistent with previous reports describing severe pulmonary hypertension with SLE, the patients in this study did not have significant interstitial lung disease, pulmonary emboli, or left-sided heart dysfunction, indicating that their symptoms were primarily the result of pulmonary vascular disease.

The diagnosis of SLE was well established in the six patients included in this study, and duration of...
illness did not correlate with either the development of pulmonary hypertension or the severity. The occurrence of pulmonary hypertension in patients with SLE, at a time when nonpulmonary disease activity was quiescent, has previously been reported.21,22 There were minimal signs of lupus activity at the time these six patients became symptomatic from pulmonary hypertension. Furthermore, there has been only one SLE flare during treatment with epoprostenol and no deterioration in renal function in any patient.

One third of patients with SLE have antiphospholipid antibodies, but most do not develop thromboembolic complications.23 Three of our patients had antiphospholipid antibodies, but large vessel pulmonary thromboembolic disease was excluded as the cause of pulmonary hypertension. The significance of antiphospholipid antibodies in the development of pulmonary hypertension remains to be determined.

Therapy with calcium channel blockers, efficacious in about 25% of patients with PPH,24 has not been effective in patients with SLE and pulmonary hypertension. Though there are a few anecdotal reports of improvement with corticosteroids,19,20,27 most studies have not shown any benefit. All the patients in this study had received corticosteroids for varying lengths of time, and five developed pulmonary hypertension while receiving prednisone. Immunosuppressive therapy has also been used in patients with SLE and pulmonary hypertension without significant improvement. There was a similar lack of benefit noted in the three patients in this series who were taking immunosuppressive medications.

Because approximately 70% of patients with PPH show improvement with epoprostenol therapy,28 it is not surprising that all six patients presented here showed an impressive symptomatic and clinical response to epoprostenol. Effective doses of epoprostenol appear to be similar to those found in patients with PPH. One patient has done remarkably well on a very low dose of epoprostenol (4 ng/kg/min). She has had a sustained, marked improvement in her functional status and is currently identified as NYHA class I/II. The other five patients have required regular dose increases. Presently, there is no consensus on the optimal strategy for chronic epoprostenol dosing.

These preliminary results indicate that pulmonary hypertension associated with SLE may be as responsive to epoprostenol therapy as that found in PPH. In contrast, a recent abstract reported that patients with pulmonary hypertension associated with connective tissue disease receiving epoprostenol had a 2-year survival of only 50% compared with PPH patients treated concurrently who had a 75% survival.29 Many patients in this series had scleroderma or CREST syndrome and were older than the PPH patients. Results of a multicenter study evaluating the efficacy of epoprostenol in 111 patients with the scleroderma spectrum of diseases showed no survival advantage at 12 weeks in the group receiving epoprostenol, though there were significant improvements in the 6-min walk test and in quality of life.30 Comorbid illness and failure to impact on other aspects of scleroderma/CREST syndrome likely contributed to the lack of improvement in survival.

Pulmonary vascular abnormalities of patients with SLE-associated pulmonary hypertension are histologically similar to those of patients with PPH and suggests a common pathologic process. SLE and PPH are illnesses frequently found in women of child-bearing age, which raises the possibility of shared etiologic factors. However, while the final result may be similar in genetically susceptible individuals, the initiating event in the pathologic process may be different in patients with SLE compared to patients with PPH.

In conclusion, we have presented six patients with SLE-associated pulmonary hypertension treated with chronic administration of epoprostenol. All have experienced dramatic improvement in functional status, without unexpected problems related to epoprostenol therapy. The four patients who underwent repeat right heart catheterization have shown a marked decrease in PVR. These results indicate that chronic treatment with epoprostenol may be effective and well tolerated in patients with SLE who develop marked pulmonary hypertension unrelated to fibrotic lung disease. Whether the experience in patients with SLE or other conditions associated with pulmonary hypertension will ultimately be the same as that in patients with PPH requires a longer duration of follow-up and treatment of a greater number of patients. Further evaluation of this therapy in patients with SLE and other diseases associated with pulmonary hypertension is warranted.

References
5 Salerni R, Rodnan GP, Leon DF, et al. Pulmonary hyperten-

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