Hemodynamic Effects of Epoprostenol in Patients With Systemic Sclerosis and Pulmonary Hypertension*

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Study objectives: To determine the cause of pulmonary hypertension (PH) in systemic sclerosis (SSc) patients since PH can occur because of pulmonary arteriopathy, pulmonary parenchymal destruction, and left ventricular cardiac dysfunction.

Design and setting: Consecutive case series in a university hospital.

Patients: Nine SSc patients with PH (mean pulmonary artery pressure, 41 mm Hg), with (n = 6) or without (n = 3) concomitant interstitial lung disease (ILD).

Methods: Acute infusion of epoprostenol was begun at 2 ng/kg/min and was titrated upward at a rate of 2 ng/kg/min every 30 min until symptomatic complications developed or pulmonary artery vascular resistance (PVR) was reduced by 50%.

Results: Eight of nine patients demonstrated a reduction of ≥ 20% in PVR, suggesting that vasoreactivity is common despite the presence of significant ILD. A single patient had no response to infusion with unchanged hemodynamics and oxygenation. One patient developed hypoxemia as cardiac output increased, suggesting a worsening of ventilation/perfusion matching or the presence of an anatomic shunt. Acute pulmonary edema developed in one patient at an infusion rate of 6 ng/kg/min. The results of cardiac catheterization suggested that pulmonary edema was caused by SSc heart disease.

Conclusion: SSc patients with ILD have diverse and sometimes multiple causes of PH that can be determined by short-term epoprostenol infusion. Beneficial effects can be obtained from epoprostenol despite extensive ILD.

Key words: epoprostenol; interstitial lung disease; pulmonary hypertension; systemic sclerosis

Abbreviations: dcSSc = diffuse cutaneous systemic sclerosis; HRCT = high-resolution CT; ILD = interstitial lung disease; PAOP = pulmonary artery occlusive pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; SSc = systemic sclerosis; TLC = total lung capacity

Pulmonary hypertension (PH) in systemic sclerosis (SSc) is a common1,2 and often fatal3,4 complication. Physiologically, the elevation of pulmonary artery pressure can result from pulmonary arteriopathy,5 vascular destruction from interstitial lung disease (ILD),5,6 hypoxic pulmonary vasoconstriction,7 or left ventricular myocardial8 or valvular9 dysfunction. Although strategies for pulmonary vasodilation in patients with limited cutaneous SSc and isolated PH have been reported,10–13 most patients with PH complicating SSc1,14 were excluded from those trials on the basis of concomitant ILD. The challenge in the treatment of PH in patients with SSc is to determine which patients might benefit from vasodilator medication.

Historically, when faced with SSc PH, physicians screen for isolated PH with spirometry, chest radiography, and a chest high-resolution CT (HRCT) scan to exclude significant ILD. The classic SSc patient with isolated PH is one with limited cutaneous SSc (variant with calcinosis cutis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias).15 The diagnosis is not difficult with normal spirometry, low diffusion capacity, exercise oxygen desaturation, and minimal ILD on
chest radiography or HRCT scan. Echocardiography with Doppler is performed to determine the presence and severity of PH and exclude pericardial or left ventricular dysfunction. Although exercise tests with or without Doppler echocardiography have been used to determine the likelihood of PH causing exercise intolerance, these tests do not provide information as to whether the PH is reversible, since the vasculopathy may be caused by vascular obliteration and/or vasoospasm.

Our approach to the determination of vasospastic PH has been to attempt acute vasodilation with epoprostenol in all symptomatic patients with systolic pulmonary artery pressures of > 40 mm Hg to determine reversibility. We report our consecutive case series of SSc patients with PH, the majority having ILD, who have received a diagnostic epoprostenol challenge with invasive hemodynamic monitoring.

**Materials and Methods**

We evaluated all patients with SSc and echocardiographic PH (ie, with a peak right ventricular systolic pressure of > 40 mm Hg demonstrated on Doppler echocardiography of the tricuspid regurgitation jet) referred to the pulmonary division from January 1, 1998, to July 1, 1999. Nine patients were admitted to the Medical University Hospital for systematic evaluation. All patients had received calcium channel blockers prior to evaluation for Raynaud’s phenomenon and/or PH. Each patient received an HRCT scan, ventilation/perfusion lung scan, spirometry, total lung capacity (TLC) measurement by helium dilution, and diffusing capacity of the lung for carbon monoxide. After informed consent, a Swan-Ganz catheter was placed for a systemic pressure (PAOP).

**Table 1—Steps for Epoprostenol Short-term Titration**

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient may be studied on calcium channel blockers; addition of epoprostenol will further vasodilate vasoactive PH</td>
</tr>
<tr>
<td>2</td>
<td>Wean any supplemental O₂ use to O₂ saturation of 90% or study patient on room air if possible to permit early detection of O₂ desaturation</td>
</tr>
<tr>
<td>3</td>
<td>Establish baseline hemodynamics with Swan-Ganz catheter</td>
</tr>
<tr>
<td>4</td>
<td>Initiate epoprostenol infusion at 2 ng/kg/min</td>
</tr>
<tr>
<td>5</td>
<td>Monitor systemic BP every 3 min</td>
</tr>
<tr>
<td>6</td>
<td>Obtain follow-up hemodynamics and assess side effects at 30 min</td>
</tr>
<tr>
<td>7</td>
<td>Increase infusion by 2 ng/kg/min every 30 min until side effects become limiting or PVR falls by 50%</td>
</tr>
<tr>
<td>8</td>
<td>Be alert to adverse effects such as pulmonary edema and worsening oxygenation</td>
</tr>
<tr>
<td>9</td>
<td>Slowly withdraw treatment with epoprostenol by 2 ng/kg/min every hour to assess possibility of rebound vasoconstriction</td>
</tr>
</tbody>
</table>

**Results**

Six patients with significant ILD (TLC, < 70% of predicted) seen on chest HRCT scans were studied. An additional three patients with isolated PH were studied. The demographic and spirometric variables at baseline are recorded in Table 2.

Epoprostenol infusion was well-tolerated by seven of nine patients. Patient 2, despite PVR improvement, developed hypoxemia that did not improve with the use of supplemental oxygen and that continued until the cessation of epoprostenol administration. Patient 4 developed pulmonary edema at an infusion rate of 6 ng/kg/min that was associated with an increase in PAOP from 12 to 36 mm Hg without ischemia on electrocardiography. Subsequent cardiac catheterization demonstrated normal epicardial coronary arteries but a global reduction in ejection fraction to 40%. Echocardiography showed diastolic dysfunction.

Side effects, including rebound PH, have been described following withdrawal of epoprostenol therapy. One of our patients had asymptomatic worsening of pulmonary artery pressures to values higher than baseline after stepwise drug therapy withdrawal every 30 min. Of more concern was an unusual reaction of abdominal myoclonus that involved the left half of the abdominal musculature in a second patient. Although far from definitive, the neurologic examination suggested local vasospasm of peripheral arteries rather than a CNS cause. Thereafter, a 1-h duration was used for incremental drug therapy withdrawal in 2-kg/min increments without complications.

PVR decreased by > 20% in eight of nine patients studied (Table 3). The patient without improvement had extensive honeycombing seen on HRCT. The presence of honeycombing, however, did not preclude a beneficial hemodynamic response to epoprostenol in four patients.

Long-term survival trended toward improvement with the short-term use of epoprostenol and the absence of ILD. Four of five patients who received longitudinal epoprostenol infusion were alive at a
mean of 18 months, while three of four patients not receiving epoprostenol died ($p = 0.10$). Additionally, four of six patients who had ILD died, and none of the patients without ILD died ($p = 0.06$).

Patient 1, with the lowest TLC, had no response to short-term infusion, implying that PH was caused by a fixed arteriopathy secondary to ILD. Patient 2 had a detrimental response to oxygenation. Patient 4, who developed pulmonary edema on short-term infusion, was begun on a regimen of long-term infusion of epoprostenol and tolerated doses of 3 to 5 ng/kg/min with decreased dyspnea. On two occasions, she developed symptoms of increased dyspnea and cough when her infusion was increased from 5 to 6 ng/kg/min. On those occasions, her dyspnea improved with a decrease in dose. She ultimately died after 6 months of epoprostenol therapy with right heart failure and possible sepsis that were precipitated by Stevens-Johnson syndrome secondary to trimethoprim-sulfamethoxazole administration.

**Discussion**

Secondary PH is a heterogeneous condition in patients with SSc. This case series confirms that ILD, pulmonary artery vasculopathy with vasospasm, or left ventricular dysfunction can all contribute to the disorder. Traditional teaching has suggested that only patients with limited cutaneous SSc without ILD have vasoreactive PH. Had therapy been limited to those patients without ILD, the majority of our patients would have been denied therapy. The ability to find vasoreactivity in five of six patients with ILD extends the possibility of benefit to a larger group of SSc patients.

### Table 3—Hemodynamics and Outcome Following Epoprostenol Infusion*

<table>
<thead>
<tr>
<th>Patient</th>
<th>RA, mm Hg</th>
<th>Epoprostenol Baseline</th>
<th>CO, L/min</th>
<th>PVR, dyne * s * cm⁻²</th>
<th>ΔO₂ Sat</th>
<th>Long-term Use</th>
<th>Outcome (mo)</th>
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<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>26 (−13)</td>
<td>7.0</td>
<td>6.4 (−9)</td>
<td>228</td>
<td>225 (0)</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>55 (+6)</td>
<td>3.9</td>
<td>5.9 (+51)</td>
<td>656</td>
<td>427 (−35)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>48 (−4)</td>
<td>2.8</td>
<td>4.2 (+50)</td>
<td>656</td>
<td>427 (−35)</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>59 (+40)</td>
<td>3.5</td>
<td>5.8 (+65)</td>
<td>685</td>
<td>317 (−54)</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>26 (−19)</td>
<td>4.5</td>
<td>6.2 (+38)</td>
<td>362</td>
<td>165 (−54)</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>32 (−27)</td>
<td>4.2</td>
<td>5.4 (+29)</td>
<td>690</td>
<td>443 (−36)</td>
<td>Yes</td>
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### Table 2—Demographics of SSc patients with PH*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Years With SSc</th>
<th>Type</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Pack-Years</th>
<th>FVC, L</th>
<th>TLC, L</th>
<th>DLCO, mL/min/mm Hg</th>
<th>D/VA</th>
<th>NYHA Class</th>
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<tr>
<td>1</td>
<td>8</td>
<td>lcSSc</td>
<td>51</td>
<td>F</td>
<td>0</td>
<td>1.42</td>
<td>1.89</td>
<td>4.3 (23)</td>
<td>3.07 (72)</td>
<td>III</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>dcSSc</td>
<td>56</td>
<td>F</td>
<td>105</td>
<td>1.69</td>
<td>2.59</td>
<td>6.9 (36)</td>
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<td>3</td>
<td>23</td>
<td>lcSSc</td>
<td>58</td>
<td>M</td>
<td>80</td>
<td>3.10</td>
<td>4.33</td>
<td>4.3 (16)</td>
<td>1.08 (26)</td>
<td>III</td>
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<td>4</td>
<td>3</td>
<td>dcSSc</td>
<td>46</td>
<td>F</td>
<td>0</td>
<td>1.39</td>
<td>4.28</td>
<td>8.9 (47)</td>
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<td>5</td>
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*lcSSC = limited cutaneous SSc; FVC = forced vital capacity; DLCO = diffusing capacity of the lung for carbon monoxide; D/VA = DLCO indexed to alveolar volume; NYHA = New York Heart Association; F = female; M = male. Values in parentheses are percent predicted.
patients. Since SSc without skin findings (SSc sine scleroderma)\(^1\) may be a common diagnosis hiding within the population of patients with idiopathic pulmonary fibrosis, the lessons from SSc may be valuable in all patients with dyspnea and ILD.

ILD is common in patients with diffuse cutaneous SSc (dcSSc) and is not uncommon in those with limited cutaneous disease. Autopsy series and evaluations with HRCT scanning in patients with dcSSc\(^2\) have demonstrated that most patients have abnormalities in the lung parenchyma.\(^3\) The temptation is to ascribe dyspnea to these abnormalities.

Exercise tests with exhaled gas analysis in SSc patients have demonstrated a vascular abnormality in the majority of patients with dyspnea.\(^4\) Unfortunately, a site-specific determination of the vascular abnormality is not possible since the hallmark of a decreased anaerobic threshold can occur with cardiac disease, peripheral vascular disease, or pulmonary vascular disease that limits cardiac output, all of which can be seen in SSc.

Our experience suggests that some SSc patients with significant degrees of secondary PH should not receive long-term epoprostenol therapy. Instead of giving the medication to every patient with secondary PH, beneficial short-term effects can be used to guide which patients are likely to have improved conditions from this expensive medication. Since benefits have been demonstrated in patients with secondary PH from diverse causes, a short-term trial of epoprostenol appears to be a more rational strategy to determine responders than reliance on patient demographics to determine the likelihood of response. Since the epoprostenol response occurred in all patients who were taking calcium channel blockers, responsiveness or lack of responsiveness to a calcium channel blocker does not appear to be sensitive enough to predict an epoprostenol response.

A growing body of evidence in primary PH suggests that long-term epoprostenol therapy may be associated with remodeling of the pulmonary vasculature and with a further reduction in PVR over time, even in patients without an acute vasodilator response.\(^5\) Klings et al\(^6\) recently published the Boston University experience with PH in patients with SSc, finding that 13 of 16 patients had an acute vasodilator response, which was defined as a 25% reduction in PVR in response to epoprostenol. When combined with our series in which eight of nine patients responded in the short term, we would suggest that an SSc patient cohort without an acute vasodilator response to aggressive epoprostenol challenge would be difficult to assemble.

The physician administering epoprostenol for initial therapy for PH should be aware of the significant side effects that can occur in this patient population. We interpret the significant oxygen desaturation that occurred in patient 2 as likely to be secondary to intrapulmonary shunting, as has been reported previously in primary PH.\(^7\) In that case series of two patients, contrast echocardiography showed a delayed appearance of bubbles in the left cardiac chambers after peripheral venous injection, suggesting an anatomically significant shunt in the lung periphery. In our patient with honeycomb lung who was receiving oxygen therapy, an alternative possibility of severely worsened ventilation/perfusion matching remains. Since worsening of oxygenation can be a clinically significant event, epoprostenol infusion should be evaluated without routine oxygen administration, provided that oxygen saturation is in the normal range and can be followed serially. This allows for an objective assessment of oxygenation on a more steep portion of the oxyhemoglobin dissociation curve.

One patient developed pulmonary edema during epoprostenol infusion, which manifested as an elevation of PAOP, diffuse alveolar infiltrates, and oxygen desaturation. Pulmonary edema with epoprostenol infusion has been described previously in patients with pulmonary veno-occlusive disease,\(^8\) pulmonary capillary hemangiomatosis,\(^9\) and scleroderma,\(^10\) all of which are conditions in which obstruction to flow occurs beyond the pulmonary capillaries. A single case report of veno-occlusive disease in patients with SSc has been reported.\(^11\) We believe that pulmonary edema may occur in SSc patients because left ventricular compliance is reduced by SSc cardiac disease\(^11\) such that the left side of the heart may not accommodate the increased flow from the right side of the heart that occurs with epoprostenol therapy. The cardiac fibrosis that occurs is thought to be secondary to small-vessel spasm and/or obliteration leading to characteristic contraction band necrosis. A noninvasive means of diagnosis for SSc myocardial disease remains problematic, unless overt diastolic dysfunction is seen on echocardiography with or without exercise, as occurred in our patient. Exercise tolerance in our patient improved following epoprostenol infusion at a dose below that initially produced pulmonary edema.

A beneficial response to prostacyclin derivatives has been reported previously in SSc patients with isolated PH. Menon et al\(^12\) demonstrated the acute effects of epoprostenol in seven patients with normal chest CT scans demonstrating vasoactivity similar to those patients in this series. A randomized, controlled trial sponsored by Glaxo Wellcome for epoprostenol approval in patients with PH secondary to connective tissue diseases has been published,\(^13\) showing improved hemodynamics in patients receiv-
ing epoprostenol therapy. McLaughlin et al\textsuperscript{13} recently reported on an initial experience in patients with secondary PH, the results of which suggested epoprostenol efficacy in some patients with connective tissue disease. Experience with scleroderma patients without ILD has suggested sustained improvement with epoprostenol therapy in those with SSc.\textsuperscript{23}

The diagnostic algorithm we used has not been published previously (to our knowledge). Although the 50% PVR reduction chosen to stop titration is very high, our philosophy is that we would rather monitor side effects in an ICU setting than on outpatient titration. Surveys have suggested a wide spectrum of algorithms for the evaluation and treatment of PH from epoprostenol therapy.\textsuperscript{32} Since side effects were seen within 10 min of rate increases in all of our patients, the upward dose titration for efficacy and safety might be able to be shortened in a manner similar to the protocols of Menon et al\textsuperscript{12} and Klings et al,\textsuperscript{23} which used 15-min increments.

Another impact of the results of our series may be an expansion of the number of patients that may potentially be helped by epoprostenol therapy. We found no clinical factors that reproducibly predicted a lack of response to treatment. The ability to predict epoprostenol responsiveness from the response to calcium channel blockade,\textsuperscript{10} angiotensin-converting enzyme inhibitors,\textsuperscript{11} inhaled nitric oxide,\textsuperscript{33} or adenosine\textsuperscript{34} appears to be an inexact science, leaving an ICU admission as the only effective way to screen for treatment-responsive PH. Factors that might predict the development of PH, such as routine exercise echocardiography or CT density grading schemes,\textsuperscript{35} might be developed in future studies. However, once a diagnosis of PH is established, the majority of patients still respond to epoprostenol therapy.

We recognize that the major limitation to our observation is the lack of long-term invasive follow-up. Since our series was not randomized and included a small number of patients, any benefits for survival are speculative. Historic control subjects with SSc PH have recorded a 2-year survival rate with calcium channel blocker therapy of 40% and a 5-year survival rate of 10%.\textsuperscript{3}

The short-term use of epoprostenol may be challenged in some circles since invasive monitoring and hospitalization are necessary. With the recognition that static pulmonary artery pressures do not reflect the variability in pulmonary artery tone that occurs throughout the day,\textsuperscript{36} many centers have transitioned to exercise echocardiography to determine a more dynamic evaluation of PH. The value of this intervention is the ability to diagnose the left ventricular or valvular dysfunction that occurs with exercise. Unfortunately, pulmonary artery pressures will increase independently of whether vascular bed destruction or a vasospastic component is present.

In summary, we present a consecutive case series of patients with SSc and secondary PH whose management included a diagnostic epoprostenol challenge. The acute effects of epoprostenol contributed to a thoughtful and patient-specific approach to therapy in a group of patients with a difficult disease.

**REFERENCES**

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