Pulmonary vascular reactivity in severe pulmonary hypertension associated with mixed connective tissue disease

Philippe Jolliet, Jean-Benoit Thorens, Jean-Claude Chevrolet

Abstract
Pulmonary vascular reactivity tests were performed in a young woman with mixed connective tissue disease and severe pulmonary hypertension. Vasoreactivity was documented in response to intravenous prostacyclin (PGL₂), oral nifedipine, and inhaled nitric oxide, with quantitative differences. Nitric oxide produced a moderate lowering of pulmonary arterial pressure and resistance without any deleterious systemic effect. The use of nitric oxide in testing for pulmonary vasoreactivity merits further evaluation. (Thorax 1995;50:96-97)

Keywords: pulmonary vascular reactivity, pulmonary hypertension, mixed connective tissue disease, nitric oxide.

Pulmonary hypertension in mixed connective tissue disease is often resistant to immunosuppressive agents. Treatment with vasodilators might be the only option to improve survival, and they have been shown to be effective in mixed connective tissue disease. The prerequisite to initiating treatment is that vasoreactivity must be preserved. However, testing with vasodilators that have systemic effects can produce severe complications. Nitric oxide could represent an alternative as it is devoid of these effects when inhaled. This case report documents the use of nitric oxide for such a purpose in a patient with mixed connective tissue disease.

Case report
A 31 year old woman presented with asthenia, weight loss (5 kg), dryness of mouth and eyes, dysphagia, Raynaud’s phenomenon, lower limb myalgias, progressive dyspnoea, and retrosternal pain.

On physical examination she was afebrile, heart rate 84/min, blood pressure 130/80 mm Hg. There was salivary gland hypertrophy, no clubbing, multiple, bilateral, lymphadenopathy, no inspiratory crackles with an enlarged, non-tender liver and spleen. Laboratory examination showed erythrocyte sedimentation rate of 100 mm/h, protein 103 g/l, IgG 55.7 g/l (normal 7-5-10.5 g/l), no para-proteinemia, AST/ALT 71/54 IU/l (<32/36), lactate dehydrogenase 686 IU/l (<412). Rheumatoid factor, antinuclear and antiribonucleoprotein antibodies were positive (titres of 1:320, 1:40000 and 1:1024, respectively); anti-DNA, anti-Jo1, anti-Scl-70, antisalivary gland, anti-Sm-protein, and anti-neutrophil cytoplasmic antibodies were negative. The chest radiograph showed cardiomegaly with normal lung parenchyma. Electrocardiogram showed sinus rhythm, right axis deviation and T wave inversion in leads V1-V4. The isotopic ventilation/perfusion lung scan was normal; arterial blood gases (room air) were pH 7.44/Paco₂ 9.67 kPa/Paco₂ 4.0 kPa/Sao₂ 95%. Pulmonary function tests were normal apart from the carbon monoxide transfer factor (TLco) 5.3 mmol/kPa/min (predicted 8-6). Cervical lymph node biopsy showed non-specific hyperplasia.

Mixed connective tissue disease was diagnosed. Vasodilator tests were performed. Pulmonary (PAP) and systemic (PAS) blood pressures were continuously monitored and graphically recorded. Pulmonary (PVR) and systemic (SVR) vascular resistance were com-

<table>
<thead>
<tr>
<th>Protacyclin</th>
<th>Nifedipine</th>
<th>Nitric oxide</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>Max effect (%)</td>
<td>Baseline</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diastolic</td>
<td>62</td>
<td>70</td>
</tr>
<tr>
<td>systolic</td>
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<td>109</td>
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<tr>
<td>mean</td>
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<tr>
<td>PAP (mm Hg)</td>
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<tr>
<td>diastolic</td>
<td>68</td>
<td>61</td>
</tr>
<tr>
<td>systolic</td>
<td>116</td>
<td>109</td>
</tr>
<tr>
<td>mean</td>
<td>84</td>
<td>76</td>
</tr>
<tr>
<td>SVR (dyn.s.cm⁻¹)</td>
<td>1045</td>
<td>576</td>
</tr>
<tr>
<td>PVR (dyn.s.cm⁻¹)</td>
<td>412</td>
<td>208(49-5)</td>
</tr>
</tbody>
</table>

Max effect = maximum effect obtained with the drug tested expressed as (%) decrease for PVR and PAP mean; SAP = systemic arterial pressure; PAP = pulmonary arterial pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.
Nitric oxide concentration (ppm) is indicated in bold numbers. Upper arrows show the initial drop and rebound occurring approximately 30 seconds after the beginning of inhalation. Tracing speed 5 mm/min.

Discussion

Vasoreactivity was present with all three vasodilators with quantitative differences. PGI₂ produced larger decreases in PAPm and PVR than nifedipine (table). However, the baseline values were much lower for nifedipine than for PGI₂. The short half-life of PGI₂ (1–2 minutes) should preclude any residual effect of the drug 24 hours later. However, we have recently documented major spontaneous variations in PVR (up to 32%) in patients with chronic pulmonary hypertension, during 72 hour measurements. This could account for the differences observed in our patient. Nitric oxide decreased PVR by approximately 50% in patients with chronic pulmonary hypertension at an inspired concentration of 40 ppm. Using the same concentration we observed a much smaller decrease (14%), but the baseline PVR in our patient was much lower.

The figure shows that, with all concentrations used, a transient drop in PAP occurred less than 30 seconds after the start of inhalation, followed by a rebound to baseline values and a slow decrease. This could be due to a reflex vasoconstriction compensating for the initial vasodilating effect of nitric oxide, but subsequently overridden by it. Furthermore, seconds after nitric oxide was discontinued a significant rebound was witnessed. This could stem from pulmonary vascular hyperreactivity, as in systemic hypertension, increased circulating catecholamines, or intracellular down-regulation to the effects of nitric oxide. No such overshoot occurred after PGI₂ or nifedipine.

In conclusion, pulmonary vascular reactivity to nitric oxide in mixed connective tissue disease was documented without adverse systemic effects. Thus, even though only those vasodilators that also exhibit these side effects can be used for long term therapy at present, nitric oxide could represent a useful and safer test agent for vasoreactivity and should be studied further. The overshoot in PAP after discontinuation of nitric oxide merits a note of caution.

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