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

Philippe Jolliet, Jean-Benoît 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 (PGI₂), 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.^{1,2} Treatment with vasodilators might be the only option to improve survival,³ and they have been shown to be effective in mixed connective tissue disease.⁴ The prerequisite to initiating treatment is that vasoreactivity must be preserved.³ However,

testing with vasodilators that have systemic effects can produce severe complications.⁵ 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 7.5-16.2 g/l), no paraproteinaemia, AST/ALT 71/54 IU/l (<32/36), lactate dehydrogenase 686 IU/l (<412). Rheumatoid factor, antinuclear and anti-ribonucleoprotein 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/PaO₂ 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-

Medical Intensive Care Unit
P Jolliet
J-B Thorens
J-C Chevrolet

Division of Pneumology
J-B Thorens

University Hospital, Geneva, Switzerland

Reprint requests to:
Dr P Jolliet, Soins Intensifs de Médecine, Hôpital Cantonal Universitaire, 24, Rue Micheli-du-Crest, 1211 Genève 14, Switzerland.

Received 30 September 1993
Returned to authors 14 December 1993
Revised version received 4 January 1994
Accepted for publication 6 January 1994

Results of vasodilator tests

	Prostacyclin		Nifedipine		Nitric oxide	
	Baseline	Max effect (%)	Baseline	Max effect (%)	Baseline	Max effect (%)
Haemodynamic values:						
Heart rate (n/min)	73	75	71	84	84	83
Cardiac output (l/min)	6.2	10.0	6.3	10.6	7.7	7.8
SAP (mm Hg)						
systolic	116	108	109	94	122	120
diastolic	68	61	61	51	79	68
mean	84	77	76	63	85	81
PAP (mm Hg)						
systolic	65	55	42	37	55	44
diastolic	22	18	19	17	26	23
mean	37	31(16.2)	28	25(10)	37	29(21.2)
SVR (dyn.s.cm ⁻⁵)	1045	576	926	465	851	810
PVR (dyn.s.cm ⁻⁵)	412	208(49.5)	215	172(20)	322	276(14.2)
Arterial blood gases (room air):						
pH	7.43	7.44	7.45	7.45	7.45	7.45
PaCO ₂ (kPa)	3.6	3.2	3.2	3.6	3.5	3.6
PaO ₂ (kPa)	11.7	12.8	13.8	11.0	13.3	10.2
SaO ₂ (%)	97	97	98	97	98	96

Max effect = maximum effect obtained with the drug tested expressed as (%) decrease for PVR and PAPmean; SAP = systemic arterial pressure; PAP = pulmonary arterial pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

Graphic recording of pulmonary artery pressure during nitric oxide inhalation. Lower black and striped arrows indicate start and stop, respectively, of nitric oxide inhalation. 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.

puted by standard equations. The response was considered positive if mean PAP (PAPm) and/or PVR decreased by $\geq 20\%$ of baseline. A prostacyclin (PGI_2 , Flolan, Wellcome) infusion, 1 ng/kg/min, was initiated and increased by increments of 1 ng/kg/min. At 6 ng/kg/min the test was stopped (table). The next day oral nifedipine was given. After an initial dose of 10 mg, a dose of 20 mg was administered hourly. After a cumulative dose of 50 mg nausea and symptomatic hypotension occurred. Upon return to baseline conditions nitric oxide was administered. The patient was equipped with a noseclip and a tight-fitting mouthpiece connected to a one-way Hans-Rudolf pneumatic valve. A pneumotachograph (Fleisch No. 8) measured total minute ventilation. Nitric oxide was delivered for five minutes at 12 ppm, then for two 10-minute periods each at 24 and 40 ppm. Maximum effect occurred at 24 ppm, without systemic effects (table). PAP decreased within seconds of starting nitric oxide, while rebound followed its cessation (figure).

A single bolus injection of cyclophosphamide (1000 mg), and methylprednisolone 250 mg twice daily for three days, were administered. The patient was discharged on oral prednisone 60 mg/day and nifedipine, 20 mg three times daily.

Discussion

Vasoreactivity was present with all three vasodilators with quantitative differences. PGI_2 produced larger decreases in PAPm and PVR than nifedipine (table). However, the baseline values were much lower for nifedipine than for PGI_2 . The short half-life of PGI_2 (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.⁶ 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.⁷ Using the same concentration we observed a much smaller decrease (14%), but the baseline PVR in our patient was much lower.⁷

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,⁸ increased circulating catecholamines, or intracellular down-regulation to the effects of nitric oxide.⁹ No such overshoot occurred after PGI_2 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.

- 1 Dahl M, Chalmers A, Wade J, Calverley D, Munt B. Ten year survival of a patient with advanced pulmonary hypertension and mixed connective tissue disease treated with immunosuppressive therapy. *J Rheumatol* 1992;19:1807–9.
- 2 Bennett RM. Mixed connective tissue disease and other overlap syndromes. In: Kelly WN, Harris ED, Ruddy S, Sledge CB, eds. *Textbook of rheumatology*. 3rd edn. Philadelphia: WB Saunders, 1989: 1147–65.
- 3 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327:76–81.
- 4 Alpert MA, Pressly TA, Mukerji V, Lambert CR, Mukerji B, Panayiotou H, et al. Acute and long-term effects of nifedipine on pulmonary and systemic hemodynamics in patients with pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease. *Am J Cardiol* 1991;68:1687–91.
- 5 Partanen J, Nieminen M, Loumanmäki K. Death in a patient with primary pulmonary hypertension after 20 mg of nifedipine. *N Engl J Med* 1993;329:812.
- 6 Chevrolet JC, Schmid F. "Spontaneous" variability of pulmonary haemodynamics during vasodilator tests in pulmonary precapillary hypertension. *Eur J Int Med* 1992;3: 305–17.
- 7 Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Walwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet* 1991;338:1173–4.
- 8 Fiorentini C, Barbieri P, Galli C, Loaldi A, Tamborini G, Tosi E, et al. Pulmonary vascular overreactivity in systemic hypertension. *Hypertension* 1985;7:995–1002.
- 9 Moncada S, Palmer RMJ, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 1991; 43:109–42.