

## Short papers

# Nitric oxide and prostacyclin as test agents of vasoreactivity in severe precapillary pulmonary hypertension: predictive ability and consequences on haemodynamics and gas exchange

Philippe Jolliet, Pierre Bulpa, Jean-Benoît Thorens, Marc Ritz, Jean-Claude Chevrolet

### Abstract

**Background** – In patients with primary pulmonary hypertension who respond to vasodilators acutely, survival can be improved by the long term use of calcium channel blockers. However, testing for such a response with calcium channel blockers or prostacyclin (PGI<sub>2</sub>) may cause hypotension and adversely affect gas exchange. Nitric oxide (NO), which does not have these effects, could be a better test agent.

**Methods** – NO (10, 20, and 40 ppm for 15 minutes), PGI<sub>2</sub> (1–>10 ng/kg/min), and oral nifedipine (10 mg, then 20 mg/h) were administered sequentially to 10 patients after determination of the 24 hour spontaneous variability of their pulmonary and systemic mean arterial pressures. Patients were considered responders if the mean pulmonary artery pressure or pulmonary vascular resistance decreased by 20% or more.

**Results** – Six patients (60%) responded to all three agents, and three to none of the agents. One patient responded to PGI<sub>2</sub> only. In those who responded to vasodilators, NO had no major effect on gas exchange or systemic haemodynamics, while PGI<sub>2</sub> and nifedipine both induced systemic hypotension (mean (SD) systemic arterial pressure 72 (14) versus 89 (19) mm Hg with PGI<sub>2</sub> and 72 (15) versus 86 (17) mm Hg with nifedipine,  $p < 0.05$ ) and hypoxaemia (PaO<sub>2</sub> 8.7 (1.4) versus 10.8 (1.0) kPa with PGI<sub>2</sub> and 8.6 (1.4) versus 10.2 (1.5) kPa with nifedipine,  $p < 0.05$ ) and increased venous admixture (28 (9) versus 14 (4)% with PGI<sub>2</sub> and 22 (9) versus 13 (5)% with nifedipine,  $p < 0.05$ ).

**Conclusions** – NO inhalation can accurately predict a vasodilator response to nifedipine in patients with severe pulmonary hypertension without adverse effects on systemic haemodynamics and gas exchange. This absence of side effects

may make it a more appropriate agent for testing the vasodilator response.

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Keywords: pulmonary hypertension, vasodilators, nitric oxide, prostacyclin, calcium channel blockers.

In patients with primary pulmonary hypertension an improvement in survival can be obtained by the long term administration of calcium channel blockers to those who respond to vasodilators given acutely.<sup>1</sup> Calcium channel blockers have been used for this test procedure, but their effect on systemic haemodynamics can induce severe or even life threatening effects.<sup>2</sup> Because of its short half life and pulmonary vasodilator effect, prostacyclin (PGI<sub>2</sub>) has been administered instead and is regarded as the screening agent of choice.<sup>3</sup> However, PGI<sub>2</sub> is an equally potent systemic vasodilator and may impair pulmonary hypoxic vasoconstriction with resulting hypoxaemia. Recent studies have suggested that nitric oxide (NO), a selective pulmonary vasodilator, may be a better screening agent.<sup>4,5</sup> The purpose of the present study was to evaluate the ability of NO to predict a response to calcium channel blockers, and to compare its effects on haemodynamics and gas exchange with those of PGI<sub>2</sub>.

### Methods

Patients were referred after complete cardiopulmonary evaluation with right heart catheterisation indicated the presence of precapillary pulmonary hypertension, defined as a mean pulmonary artery pressure (PAP) exceeding 25 mm Hg at rest<sup>6</sup> without left ventricular failure. The study was approved by the ethics committee of our institution and informed consent was obtained from the patients.

A flow directed pulmonary artery catheter and a radial arterial catheter were inserted. Cardiac output (CO) was determined by the thermodilution method. Arterial and mixed

Medical ICU Division  
P Jolliet  
P Bulpa  
J-B Thorens  
M Ritz  
J-C Chevrolet

Division of  
Pneumology  
P Bulpa  
J-B Thorens  
University Hospital,  
Geneva, Switzerland

Correspondence to:  
Dr P Jolliet, Soins intensifs  
de Médecine, Hôpital  
Cantonal Universitaire,  
1211 Geneva 14,  
Switzerland.

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Table 1 Individual responses to vasodilating agents

Patient no.	NO	Dose* (ppm)	$\Delta$ PAP (%)	$\Delta$ PVR (%)	PGI <sub>2</sub>	Dose* (ng/kg/min)	$\Delta$ PAP (%)	$\Delta$ PVR (%)	Nifedipine	Dose* (mg)	$\Delta$ PAP (%)	$\Delta$ PVR (%)
1	+	20	-22	-26	+	6	-16	-50	+	50	-11	-34
2	+	20	-41	-44	+	6	-28	-61	+	10	-32	-53
3	-	40	-11	-16	-	10	0	-10	-	110	+9	+22
4	+	40	-22	-36	+	10	-12	-42	+	10	-18	-38
5	+	20	-23	+5	+	10	-21	-20	+	30	-18	-24
6	+	40	-7	-21	+	8	-3	-20	+	20	-8	-35
7	+	20	-21	-35	+	6	-21	-54	+	30	-30	-39
8	-	40	+2	-1	-	10	+2	-17	-	15	+6	-0
9	-	40	-2	+17	-	10	+12	-8	-	30	+5	-6
10	-	40	0	0	+	10	-4	-38	-	30	-12	-13
No of responders	6				7				6			
Mean (SD)		32 (10)	-15 (13)	-16 (20)		9 (2)	-9 (12)	-32 (19)		34 (30)	-11 (14)	-22 (22)

PGI<sub>2</sub>=prostacyclin;  $\Delta$ PAP and  $\Delta$ PVR=change in mean pulmonary artery pressure and pulmonary vascular resistance induced by the agent; +=responder; -=non-responder.

\*Dose required to obtain a significant effect in responders and maximal administered dose in non-responders. For definition of response, see text.

venous blood samples were collected simultaneously for blood gas determinations. Derived variables were computed according to standard equations.

Since a previous study from our ICU demonstrated a 24 hour variability of 11% in mean PAP and 14% in pulmonary vascular resistance (PVR) in patients with pulmonary hypertension, in the absence of any drug administration,<sup>7</sup> these parameters were first recorded every hour for 24 hours without any pharmacological intervention. The mean 24 hour variability was defined as the coefficient of variation of these measurements. NO was administered at inhaled concentrations of 10, 20, and 40 ppm, each for 15 minutes, using a previously described technique.<sup>8</sup> Inhaled NO and NO<sub>2</sub> concentrations were monitored online by an electrochemical device (Polytron, Dräger AG, Lübeck, Germany). After a one hour period to allow a return to baseline conditions, a continuous infusion of prostacyclin (PGI<sub>2</sub>, Flolan, Wellcome Research Laboratory, Beckenham, UK) was started at an initial rate of 1 ng/kg/min, and increased by 1 ng/kg/min increments every 10 minutes up to a maximum of 10 ng/kg/min. Measurements were made when a response was obtained, side effects appeared, or if there was no response after 10 minutes at the maximum dosage. The following day patients received a loading dose of 10 mg nifedipine orally followed by 20 mg every hour. If the mean systemic arterial pressure was 75 mm Hg or less the loading dose was reduced to 5 mg and subsequent doses to 10 mg.

Response to any vasodilator was considered positive if the mean PAP and/or PVR decreased by 20% or more.<sup>9</sup> Side effects prompting interruption of drug administration included subjective intolerance, a decrease in the mean systemic arterial pressure to  $\leq 60$  mm Hg, or a lowering of arterial saturation (SaO<sub>2</sub>) to  $<90\%$ .

Comparisons between baseline measurements and those obtained with each agent were performed using a paired *t* test. A paired *t* test was used to compare baseline values before each vasodilator. The response to each vasodilator was compared with the spontaneous variability in the following manner: for each patient the difference between the highest and lowest mean PAP values obtained during the 24 hour measurement represents the maximum possible decrease in mean PAP ( $\Delta$ PAP<sub>spont</sub>) resulting from spontaneous variability. The val-

ues of  $\Delta$ PAP<sub>spont</sub> for the responders were compared with those of the decrease in mean PAP obtained with each vasodilator using a Wilcoxon signed rank test.

## Results

All results are expressed as mean (SD). Ten patients were studied, four of whom had primary pulmonary hypertension while in the others pulmonary hypertension was associated with cirrhosis and portal hypertension (2), connective tissue disease (2), thromboembolic disease (1), and HIV infection (1). All had severe pulmonary hypertension (mean PAP 49 (13) mm Hg, PVR 974 (573) dyn.s.cm<sup>-5</sup>), and eight had a low cardiac index (1.9 (0.5) l/min/m<sup>2</sup>) and increased systemic vascular resistance (SVR) (2227 (852) dyn.s.cm<sup>-5</sup>). The mean 24 hour variability in the mean PAP and PVR was 11 (3)% and 13 (5)%, respectively. All patients except patient 1 were moderately hypoxaemic (Pao<sub>2</sub> 8.9 (1.2) kPa) and had increased QvA/QT (18 (8)%). Three patients (nos 4, 6, and 8) were receiving supplemental oxygen.

There was no difference between baseline values before administration of the three agents, except for a small but significant difference in heart rate between NO and PGI<sub>2</sub> (80 (13) beats/min before NO and 73 (9) beats/min before PGI<sub>2</sub>). The individual responses to the three vasodilators are indicated in table 1, together with the dose of the agent required to obtain that effect. Six patients responded to all three agents (60%) while three responded to none (30%). Patient 10 responded to PGI<sub>2</sub> only.

All results hereafter refer to the group of 10 patients, and the values obtained with each vasodilator are compared with baseline values documented prior to testing with that particular vasodilator. Mean PAP was lowered by NO (41 (10) versus 49 (12) mm Hg,  $p<0.01$ ) and nifedipine (42 (15) versus 48 (14) mm Hg,  $p<0.04$ ). PVR decreased with NO (798 (460) versus 974 (563) dyn.s.cm<sup>-5</sup>,  $p<0.01$ ) and nifedipine (757 (376) versus 1008 (570) dyn.s.cm<sup>-5</sup>,  $p<0.01$ ). PGI<sub>2</sub> decreased only the PVR (650 (366) versus 948 (435) dyn.s.cm<sup>-5</sup>,  $p<0.003$ ). Heart rate was decreased by NO (74 (10) versus 80 (13) beats/min,  $p<0.05$ ), increased by PGI<sub>2</sub> (84 (9) versus 73 (9) beats/min,  $p<0.001$ ), and unaltered by nifedipine. PGI<sub>2</sub> increased the cardiac index (3.2 (1.4)

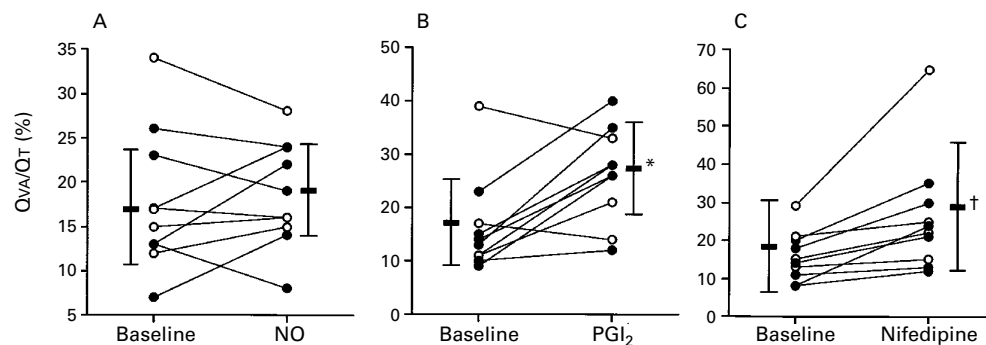


Figure 1 Effect of (A) nitric oxide (NO), (B) prostacyclin (PGI<sub>2</sub>), and (C) nifedipine on venous admixture (QVA/QT) in responders (●) and non-responders (○) showing individual responses and mean (SD). \*  $p < 0.01$ ; †  $p < 0.02$  versus baseline values.

versus 2.2 (0.9) l/min/m<sup>2</sup>,  $p < 0.002$ ). Mean SAP was decreased by PGI<sub>2</sub> (72 (14) versus 89 (19) mm Hg,  $p < 0.001$ ) and nifedipine (72 (15) versus 86 (17) mm Hg,  $p < 0.003$ ). SVR was decreased by PGI<sub>2</sub> (1052 (390) versus 1887 (737) dyn.s.cm<sup>-5</sup>,  $p < 0.001$ ) and nifedipine (1331 (604) versus 1860 (750) dyn.s.cm<sup>-5</sup>,  $p < 0.002$ ). Pao<sub>2</sub> was lowered by PGI<sub>2</sub> (8.7 (1.4) versus 10.8 (1) kPa,  $p < 0.01$ ) and nifedipine (8.6 (1.4) versus 10.2 (1.5) kPa,  $p < 0.01$ ). QVA/QT was markedly increased with PGI<sub>2</sub> and nifedipine in all patients, whereas with NO there was no significant variation for the group, even though QVA/QT did increase in three patients (fig 1).

In responders the decrease in mean PAP with each vasodilator was significantly different from spontaneous variability ( $\Delta$ PAP<sub>spont</sub> 12 (5)% versus 23 (10)% with NO, 17 (7)% with PGI<sub>2</sub>, and 20 (9)% with nifedipine,  $p < 0.05$ ).

NO inhalation was well tolerated in all patients. With PGI<sub>2</sub> patients 3 (non-responder), 4 and 6 (responders) complained of moderate chest tightness, slight throbbing headache, and a flushing sensation. Nifedipine induced hypotension with nausea and lightheadedness in patients 1 (responder), 3 and 9 (non-responders), and hypoxaemia in patients 8 and 9 (non-responders).

## Discussion

This study confirms that NO inhalation can accurately predict the response to nifedipine without adverse consequences. In contrast, PGI<sub>2</sub> induced a substantial lowering of SVR and SAP, accompanied by a rise in cardiac index and heart rate as well as an absence of decrease in PAP and a marked increase in QVA/QT.

These results confirm those of recent studies by Sitbon *et al*<sup>4</sup> and Cockrill *et al*,<sup>5</sup> with the exception that the overall response rate of 60% to vasodilators is higher than the rates of 37% and 50% obtained in these studies. The drug dosage used in our study is consistent with the standardised protocols used in most studies.<sup>14</sup> The higher response rate may be explained by a number of factors. Firstly, the non-homogeneous nature of our study group must be considered. Our patients all had precapillary

pulmonary hypertension but only four (nos 2 and 9) had primary pulmonary hypertension as defined by the National Institute of Health Patients Registry for the Characterisation of Primary Pulmonary Hypertension.<sup>6</sup> However, over the years it has become apparent that conditions such as hepatic cirrhosis, collagen disease, and HIV infection, which were present in some of our patients, are often closely associated with primary pulmonary hypertension.<sup>10</sup> Secondly, the criteria we chose as a positive response to a given vasodilator were decreases of 20% or more in mean PAP or PVR, in line with a study by Weir *et al*.<sup>9</sup> Other studies have relied on different response criteria such as a reduction in PVR of 50% and of mean PAP by 33%,<sup>11</sup> a  $\geq 20\%$  decrease in mean PAP and PVR,<sup>1</sup> or a 30% decrease in total pulmonary resistance.<sup>4</sup> Thirdly, the duration of pulmonary hypertension before testing might have an influence on reversibility. However, this factor is difficult to account for as information on the time from onset of pulmonary hypertension in these patients was not available.

PGI<sub>2</sub> caused a substantial reduction in SVR which was accompanied by a lowering of SAP and a rise in heart rate and cardiac index, effects consistent with the known properties of the drug.<sup>12</sup> While NO had no effect on gas exchange, PGI<sub>2</sub> produced a considerable increase in QVA/QT (fig 1), as well as a concomitant fall in Pao<sub>2</sub>. This could result from increased blood flow to low ventilation-perfusion pulmonary zones by attenuating hypoxic vasoconstriction<sup>13</sup> or a rise in cardiac index.<sup>14</sup> Finally, PGI<sub>2</sub> and nifedipine had comparable effects on haemodynamics and gas exchange.

In conclusion, this study supports the existing preliminary data that, with a predictive ability at least as good or perhaps better than PGI<sub>2</sub>, NO could be a valid alternative to PGI<sub>2</sub> in testing for preserved pulmonary vaso-reactivity in patients with severe precapillary pulmonary hypertension.

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## Cellular profiles in asthmatic airways: a comparison of induced sputum, bronchial washings, and bronchoalveolar lavage fluid

V M Keatings, D J Evans, B J O'Connor, P J Barnes

### Abstract

**Background** – Analysis of bronchoalveolar lavage fluid has improved our understanding of the pathogenesis of asthma. Safety issues and access to expert resources limit this technique as a research tool. Induced sputum is a non-invasive method of collecting airway fluid which is applicable to subjects with a range of severity of airflow obstruction. The method of sputum collection and processing differs between groups. A study was undertaken to compare induced sputum with bronchoscopically collected fluid.

**Methods** – Sixteen patients with mild stable asthma underwent both sputum induction and bronchoscopic examination with bronchial washings and bronchoalveolar lavage (BAL) in random order, with each procedure being separated by an interval of 12 days. Airway fluid was processed and stained for differential cell counting.

**Results** – Induced sputum was relatively rich in neutrophils and eosinophils compared with bronchial washings and BAL fluid (mean (SE) 1.3 (0.4)%, 5.0 (2.7)%, and 36.4 (3.7)% neutrophils and 0.6 (0.1)%, 1.6 (0.6)%, and 3.3 (1.1)% eosinophils in BAL fluid, bronchial washings, and induced sputum, respectively). The proportions of cells obtained at sputum induction correlated with those in bronchial washings but not BAL fluid ( $r=0.6$  and  $0.7$  for neutrophils and eosinophils, respectively,  $p<0.05$ ). By contrast, induced

sputum had a lower proportion of lymphocytes and macrophages than bronchial washings or BAL fluid, without any correlation.

**Conclusion** – Induced sputum is rich in neutrophils and eosinophils and poor in lymphocytes, suggesting an origin in the larger airways. Induced sputum adequately reflects the findings in fluid collected by direct bronchoscopy.

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Keywords: induced sputum, bronchial washings, differential cell counts.

Airway inflammation is a characteristic feature of asthma. The use of bronchoalveolar lavage (BAL) and bronchial biopsy has provided a greater understanding of the pathogenesis of this disease.<sup>1</sup> The application of these techniques has helped to define, not only the inflammatory cell population, but also the presence of inflammatory mediators and cytokines under basal and challenge conditions.<sup>2</sup>

Collection of BAL fluid is, however, an invasive procedure with a consequent associated morbidity. For research purposes bronchoscopy is restricted to patients with mild airflow obstruction and must be performed by experienced investigators. Furthermore, there is a limit to the number of times the procedure can be undertaken and, due to the invasive nature of this procedure, it may be difficult to recruit volunteers for studies involving bronchoscopy.

Induced sputum is used to obtain airway derived fluid for diagnostic<sup>3</sup> and research

National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, UK

V M Keatings  
D J Evans  
B J O'Connor  
P J Barnes

Correspondence to:  
Dr V M Keatings,  
Education and Research  
Centre, St Vincent's  
Hospital, Dublin 4, Ireland.

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