Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome

W Budts, N Van Pelt, H Gillyns, M Gewillig, F Van de Werf, S Janssens

Abstract

Objective—To determine whether inhaled NO (iNO) can reduce pulmonary vascular resistance in adults with congenital heart disease and obstructive pulmonary hypertension or Eisenmenger syndrome.

Design—23 patients received graded doses of iNO. Pulmonary and systemic haemodynamic variables and circulating cyclic guanosine monophosphate (cGMP) concentrations were measured at baseline and after 20 and 80 ppm iNO. Patients were considered responders when total pulmonary resistance was reduced by at least 20%, and rebound was defined as a greater than 10% increase in total pulmonary resistance upon withdrawal from iNO.

Results—in response to 20 ppm iNO, total pulmonary resistance decreased in four patients (18%, 95% confidence interval (CI) 2% to 34%), while in response to 80 ppm iNO it decreased in six patients (29%, 95% CI 10% to 38%). Systemic blood pressure did not change. Withdrawal resulted in rebound in three patients (16%, 95% CI 0% to 32%) after cessation of 20 ppm iNO, and in six patients (35%, 95% CI 12% to 58%) after cessation of 80 ppm iNO. Patients with predominant right to left shunting did not respond. In all patients cGMP increased from (mean (SD)) 28 (13) µmol/l at baseline to 55 (30) and 78 (44) µmol/l after 20 and 80 ppm iNO (p < 0.05 v baseline).

Conclusions—NO inhalation is safe and is associated with a dose dependent increase in circulating cGMP concentrations. Pulmonary vasodilatation in response to iNO was observed in 29% of patients and was influenced by baseline pulmonary haemodynamics. Responsiveness to acute iNO may identify patients with advanced obstructive pulmonary hypertension and Eisenmenger syndrome who could benefit from sustained vasodilator treatment.

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Keywords: nitric oxide; pulmonary hypertension; Eisenmenger syndrome

Pulmonary hypertension is defined as a persistently raised systolic pulmonary artery pressure of more than 30 mm Hg, a mean pulmonary artery pressure of more than 20 mm Hg, and a pulmonary vascular resistance of more than 67 dynes.s.cm⁻⁵.¹ Increased filling pressure in the left heart, severe obstruction to pulmonary venous return, or thrombotic occlusion of the pulmonary venules cause pulmonary hypertension. It may also be caused by precapillary vasoconstriction associated with hypoxia or high altitude, or by systemic diseases, or exposure to toxins, including fenfluramine.² In congenital heart disease with a left to right shunt, the high flow across the pulmonary vascular bed increases shear stress and causes obstructive pulmonary hypertension. When pulmonary artery pressure exceeds systemic arterial pressure, right to left shunting results in the Eisenmenger syndrome.³ In rare cases, failure to reduce high intraterrine pulmonary vascular resistance after birth results in persistent neonatal pulmonary hypertension.

The underlying molecular mechanisms involved in the development of pulmonary hypertension remain unknown. The endothelium plays an important role in regulating pulmonary vascular tone and structure by releasing a variety of vasoactive substances.⁴ One of these substances is nitric oxide (NO),⁵ which is synthesised from L-arginine by a class of enzymes termed nitric oxide synthases (NOS). In the vessel wall, NO diffuses from the endothelium to the underlying smooth muscle cells, where it activates soluble guanylate cyclase, increases cyclic guanosine monophosphate (cGMP) concentrations, and activates a cGMP dependent protein kinase. NO/cGMP signalling results in vasorelaxation as well as in the inhibition of migration, proliferation, and matrix production of smooth muscle cells.⁶

NO/cGMP signal transduction is significantly altered in patients with pulmonary hypertension. Immunohistochemical studies on lung sections from patients with pulmonary hypertension have shown either decreased or increased NOS immunoreactivity in remodelled pulmonary arteries, which is potentially related to both the underlying aetiology and the degree of pulmonary hypertension.⁷ Reduced endothelial NO production and release have been observed in children with congenital heart disease and abnormal pulmonary haemodynamics.⁸ These observations have raised interest in treatments aimed at increasing NO availability in the lungs of patients with pulmonary hypertension.

In the adult respiratory distress syndrome, inhaled NO (iNO) has been shown to improve ventilation/perfusion mismatch.⁹ After heart transplantation or valve surgery, iNO can selectively lower pulmonary vascular resistance...
and improve the clinical outcome. Respon-
siveness to iNO may also be a prognostic
marker in patients being considered for heart
transplantation, and it is associated with
improved survival after transplantation. Phar-
macological vasodilator treatment has been
shown to be more effective in patients with pri-
mary pulmonary hypertension who responded
to iNO. In newborn infants with persistent
pulmonary hypertension, iNO reduces pulmo-
nary hypertension and provides a less invasive
therapeutic alternative to extracorporeal mem-
brane oxygenation. In children with congeni-
tal heart disease and a preoperative high left to
right shunt, iNO after corrective surgery
reduces the shunt fraction and improves
oxygenation.

No data are available of the effect of iNO on
severe obstructive pulmonary hypertension in
adult patients with congenital heart disease. We
therefore investigated whether inhalation of
NO can detect residual pulmonary vasoreactiv-
ity in adults with congenital heart disease with
either severe obstructive pulmonary hyper-
tension or Eisenmenger syndrome.

Methods

Selection of Patients with Obstructive
Pulmonary Hypertension

From the start of 1996, we enrolled in the
study 23 consecutive adult patients who had
congenital heart disease and known or sus-
pected obstructive pulmonary hypertension or
Eisenmenger syndrome. Hospital admission
was either elective for planned haemodynamic
measurements (shunt evaluation, screening for
heart–lung transplantation) or when co-
morbidity occurred. The minimum age was 16
years; an upper age limit was not defined. The
ethics committee of the University Hospital
Leuven approved the study protocol. All
patients gave informed consent.

Pulmonary and Systemic Haemodynamic
Measurements

The right femoral vein was punctured and an 8
French sheath was placed under local anaes-
thesia (lignocaine hydrochloride (lidocaine),
5 ml). A Swan-Ganz catheter with thermistor
for continuous cardiac output measurement
(Swan-Ganz CCO/VIP, 139HF75, Baxter,
Irvine, California, USA) was advanced until a
stable wedge position was achieved in either
the left or the right pulmonary artery. The correct
position of the catheter was confirmed in all
patients by the pressure curve and by fluoros-
copy.

Pulmonary artery pressure and cardiac
output were monitored on-line (Vigilance,
model VGS1, Baxter). We measured cardiac
output continuously using an intravascular
thermodilution probe. Thermodilution
measurements using injection of cold fluid
cannot provide accurate cardiac output read-
ings in the pulmonary circulation of patients
with univentricular hearts, truncus arteriosus,
or significant left to right shunts. Alternatively
the Fick method for cardiac output could be
used, although measuring oxygen consumption
during NO inhalation has not been validated.

Moreover, the obligatory repeated measure-
ments of mixed venous saturation require
frequent catheter manipulation, which may not
always be technically feasible with complex
heart abnormalities. Whenever possible, we
compared the continuous cardiac output reading
with bolus injections of cold saline and
always found a difference of less than 15%.

In the first eight patients we also measured
systemic arterial pressure continuously
through a 5 French sheath in the right femoral
artery. Because blood pressure was unchanged
during the study protocol, non-invasive auto-
matic measurements of blood pressure were
used for the remaining 15 patients.

Saturation for oxygen was monitored on-line
by transcutaneous pulse oximeter (model 504/
504P, Criticare Systems, Waukesha, Wiscon-
sin, USA). Total pulmonary resistance (mean
pulmonary artery pressure divided by cardiac
output, in Wood units), cardiac index (cardiac
output divided by body surface, in l/min/m²),
and baseline shunt fraction ([systemic satura-
tion minus mixed venous saturation]/
[pulmonary vein saturation minus pulmonary
artery saturation] (Qp/Qs)) were calculated.

NO Inhalation

NO was given through nasal prongs (Salter
Labs, Arvin, California, USA) during sponta-
neous breathing of room air. NO and NOX
(NO+NOx) were monitored continuously
using electrochemical analysis (Nitric Oxide
Dosing Unit, Dräger, Lübeck, Germany). NO
(20 and 80 ppm) were given consecutively for
10 minutes. Between the inhalation of each
dose and after the 80 ppm NO inhalation, a 10
minute recovery period was observed. Pulmo-

tary and systemic haemodynamic variables
were measured at baseline, at the end of the
inhalation of 20 ppm NO, after recovery from
20 ppm NO, at the end of the inhalation of 80
ppm NO, and finally after recovery from 80
ppm NO. Total pulmonary vascular resistance
and Qp/Qs were calculated for each time point.

Patients in whom total pulmonary vascular
resistance decreased by more than 20% after
NO inhalation were defined as responders to iNO.
Patients in whom total pulmonary resistance
increased by more than 10% after NO
withdrawal were defined as having rebound
pulmonary hypertension to iNO.

cGMP Measurements

Inhaled NO diffuses across the alveolar–
capillary membrane to stimulate soluble guani-
ylate cyclase in vascular smooth muscle cells,
resulting in increased cGMP production. Increased
cGMP production is also reflected in
 circulating serum concentrations. At each time
point after NO inhalation and recovery, serum
samples were taken for cGMP measurements,
which were done using a commercially avail-
able cGMP immunoassay (Amersham, Gent,
Belgium).

Statistical Analysis

Descriptive statistics were used to evaluate the
characteristics of the study population. Con-
tinuous variables were expressed as mean (SD)
and proportions were determined by percentages with 95% confidence intervals (CI). To evaluate changes in global haemodynamics in all patients after 20 and 80 ppm NO inhalation, repeated analysis of variance (ANOVA) testing was performed. Percentages with confidence intervals were used to describe the number of patients who responded to or showed rebound after 20 and 80 ppm NO inhalation. Significance in all cases was defined as p < 0.05.

Results

Patient Characteristics
We enrolled 23 patients (seven male and 16 female) between January 1996 and January 2000. Their mean (SD) age was 32 (19) years. Details of the underlying aetiology of the congenital heart disease are given in table 1.

Haemodynamic Measurements After Inhaled NO
The baseline haemodynamic characteristics are summarised in table 2. In one patient no data were available at 20 ppm inhalation for technical reasons. Two patients were unable to finish the complete protocol owing to subjective discomfort, and only inhaled 20 ppm NO. In 18 of 22 patients (82%, 95% confidence interval (CI) 68% to 98%) residual intracardiac shunting was detected, while 50% (95% CI 39% to 71%) presented with predominant intracardiac left to right shunts (Qp/Qs > 1/1).

When the measurements from all patients were combined, systemic and pulmonary haemodynamics remained unchanged after inhalation of 20 and 80 ppm NO (ANOVA, NS). When responsiveness to iNO was investigated in individual patients, total pulmonary vascular resistance was reduced by more than 20% in four of 22 patients (18%, 95% CI 2% to 32%) after inhalation of 20 ppm NO, and in six patients (35%, 95% CI 12% to 58%) on withdrawal from 20 ppm NO.

Responsiveness to 80 ppm iNO was only found in patients with a Qp/Qs ≤ 1/1. Total pulmonary vascular resistance remained unchanged in patients with a Qp/Qs < 1/1 (fig 1). Data on the rebound phenomenon after discontinuation of iNO were available in 19 patients receiving 20 ppm and 17 patients receiving 80 ppm. Total pulmonary vascular resistance increased by more than 10% in three patients (16%, 95% CI 0% to 32%) on withdrawal from 20 ppm NO, and in six patients (35%, 95% CI 12% to 58%) on withdrawal from 80 ppm NO. When these data are combined they show that with the higher dose of iNO residual pulmonary vasoreactivity can be demonstrated in about 30% of patients with congenital heart disease.

Correlation of cGMP Serum Concentrations After Inhaled NO

cGMP increased significantly from the baseline value of 28 (13) µmol/l to 55 (30) µmol/l at 20 ppm iNO and to 78 (44) µmol/l at 80 ppm iNO (p < 0.05, fig 2). Haemodynamic responsiveness to iNO did not correlate with changes in circulating cGMP concentrations, because the latter rose proportionately and equally with increasing iNO doses in all patients. This suggests that failure to dilate the pulmonary

Table 1

<table>
<thead>
<tr>
<th>Distribution of abnormalities</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial septal defect</td>
<td>6</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>4</td>
</tr>
<tr>
<td>Persistent arterial duct</td>
<td>2</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>2</td>
</tr>
<tr>
<td>Transposition of the great arteries + VSD</td>
<td>4</td>
</tr>
<tr>
<td>Corrected transposition of the great arteries + VSD</td>
<td>2</td>
</tr>
<tr>
<td>Persistent neonatal pulmonary hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>1</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>iNO 20 ppm</th>
<th>iNO 80 ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>72 (30)</td>
<td>71 (31)</td>
<td>70 (31)</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>89 (22)</td>
<td>89 (19)</td>
<td>89 (20)</td>
</tr>
<tr>
<td>Capillary O₂ saturation (%)</td>
<td>87 (8)</td>
<td>88 (8)</td>
<td>88 (7)</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>81 (11)</td>
<td>84 (13)</td>
<td>81 (11)</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6 (3)</td>
<td>6 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>3.9 (1.0)</td>
<td>3.9 (1.8)</td>
<td>3.6 (1.5)</td>
</tr>
<tr>
<td>TPR (Wood units)</td>
<td>16 (12)</td>
<td>16 (12)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Qp/Qs</td>
<td>1.3 (0.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are mean (SD). iNO, inhaled nitric oxide; NA, not applicable; PAP, pulmonary artery pressure; Qp/Qs, baseline shunt fraction; TPR, total pulmonary vascular resistance.
resistance vessels is not caused by impaired NO/cGMP signal transduction. In addition, in patients with rebound pulmonary hypertension to iNO no correlation was found with serum cGMP.

Discussion
NO is a potent vasodilator with an important role in the regulation of pulmonary vascular tone. We investigated whether iNO can reduce pulmonary vascular resistance in adult patients with congenital heart disease presenting with obstructive pulmonary hypertension or Eisenmenger syndrome. Mean pulmonary artery pressure and mean systemic blood pressure did not change during graded NO inhalation. In response to 20 and 80 ppm iNO, total pulmonary resistance decreased in 18% and 29% of patients, respectively. Upon withdrawal from NO, rebound pulmonary hypertension was observed in 16% and 35%, respectively. Patients with predominant intracardiac right to left shunting (Qp/Qs < 1/1) did not respond to either dose of iNO (fig 1). Circulating serum cGMP concentrations increased proportionately with increasing doses of iNO in all patients but did not correlate with responsiveness to iNO or rebound after withdrawal of NO. Thus responsiveness to iNO was observed in 30% of patients with congenital heart disease and obstructive pulmonary hypertension, and may predict further benefit from sustained vasodilator treatment.

Obstructive pulmonary hypertension in patients with congenital heart lesions is caused by increased pulmonary vascular resistance resulting from high blood flow in the pulmonary circulation. When pulmonary vascular resistance exceeds systemic vascular resistance, right to left shunting and cyanosis occur, a condition defined as the Eisenmenger syndrome. The prognosis of these patients with obstructive pulmonary hypertension is better than in patients with primary pulmonary hypertension. Medical treatment (calcium channel entry blockers, prostacyclin) for primary pulmonary hypertension is of proven clinical benefit, while the success of medical treatment in children with obstructive pulmonary hypertension remains controversial and varies with age. In older patients, treatment with calcium channel entry blockers is less beneficial and has stimulated interest in new treatments. One of these is inhalation of NO, a selective pulmonary vasodilator, which reduces the degree of pulmonary hypertension in newborn infants with persistent pulmonary hypertension. It remains unknown whether there is a similar therapeutic window for iNO in the growing group of adult patients with obstructive pulmonary hypertension or Eisenmenger syndrome.

In this study, we have for the first time investigated residual pulmonary vasoreactivity to iNO in adults with obstructive pulmonary hypertension. We documented acute responsiveness of the pulmonary vasculature to iNO in 29% of our patients—more specifically in those with a moderate predominant intracardiac left to right shunt (Qp/Qs > 1/1). Previous case reports have suggested clinical benefit of iNO in specific circumstances. For example, a 27 year old woman with Eisenmenger syndrome at 36 weeks’ gestation was treated for 48 hours with inhaled nitric oxide because of progressive refractory hypoxaemia during the second stage of labour and in the postpartum period. Nitric oxide inhalation was associated with improved oxygenation and reduced pulmonary artery pressure.

Responsiveness of pulmonary resistance vessels to iNO is theoretically dependent on three different variables: first, NO must reach the alveolar ducts or alveoli; second, NO must diffuse across the alveolar–capillary barrier; and third, target smooth muscle cells of the precapillary resistance vessels must relax upon stimulation of intracellular soluble guanylate cyclase (sGC) by iNO. Our data show that inhalation of nasal prongs can deliver sufficient NO to the lower respiratory tract and across the alveolar–capillary membrane to stimulate cytoplasmatic sGC receptors in target cells, as confirmed by raised cGMP concentrations. In patients with obstructive pulmonary hypertension and a significant residual hyperdynamic component resulting from an intracardiac left to right shunt, lack of responsiveness to iNO may reflect an already maximally vasodilated vascular bed, impeding additional relaxation. High flow through the pulmonary vascular bed causes a shear stress induced increase in NO production, which may blunt the additional vasodilator effects of iNO. Lack of responsiveness to iNO is also observed in patients with fixed pulmonary hypertension (with a high mean pulmonary artery pressure and a predominant right to left shunt), in whom pulmonary target vessels are expected to be extensively remodelled. The molecular basis of vascular unresponsiveness to iNO in these remodelled pulmonary vascular beds remains unknown but may be related to impaired signal transduction downstream of cGMP, to altered phosphodiesterase function, or to a cGMP independent mechanism.

Our observations, made in a relatively small number of patients, only allow preliminary interpretations but may generate useful ideas for future studies. Questions concerning which patients respond to iNO and what biological variables can predict responsiveness remain unresolved. In primary pulmonary hypertension, acute responders to iNO can be treated with systemic vasodilators (calcium channel entry blockers, prostacyclin). In contrast, in patients with obstructive pulmonary hypertension or Eisenmenger syndrome, vasodilator treatment with calcium channel entry blockers will lower systemic vascular resistance disproportionately more than pulmonary vascular resistance. As a result, there will be increased intracardiac right to left shunting and worsening arterial oxygen saturation. Prostacyclin may be more selective for pulmonary resistance vessels, and was reported to improve exercise tolerance in patients with primary pulmonary hypertension and in those with Eisenmenger syndrome. Continuous intravenous administration of vasodilators...
in these chronically instrumented patients may, however, increase the risk of catheter induced paradoxical embolism and infection. Our study suggests that some patients with obstructive pulmonary hypertension benefit from NO inhalation, particularly those with no pre-existing intracardiac right to left shunts and moderate intracardiac left to right shunts (Qp/Qs >1/3). NO diffusing into the bloodstream is readily bound to the haem moiety of haemoglobin in circulating red blood cells, thereby eliminating systemic vasodilatation. The absence of systemic hypotensive effects is of critical importance in these patients and they may represent a cohort with potential benefit from intensified and sustained selective pulmonary vasodilator treatment.

CONCLUSIONS

Inhalation of 20 or 80 ppm NO in patients with obstructive pulmonary hypertension or Eisenmenger syndrome is feasible and safe, and reduces total pulmonary resistance in 30% of cases. Identification of predictive factors for NO responsiveness is warranted and requires a prospective study in a larger cohort of patients with congenital heart disease and pulmonary hypertension. Responsiveness to iNO in a subset of patients suggests a therapeutic window for sustained selective pulmonary vasodilator treatment (prostacyclin or NO). Whether prolonged NO treatment can prevent the progression of obstructive pulmonary hypertension, as was recently demonstrated in experimental models, remains to be determined.

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1 Barratt-Boyes BG, Wood EH. Cardiac output and related measurements and pressure values in the right heart and associated vessels, together with an analysis of the hemodynamic response to the inhalation of high oxygen mixtures in healthy subjects. J Lab Clin Med 1958;51:72–90.
Unusual multiple spasm during coronary angioplasty

A 56 year old man was hospitalised for unstable angina. Coronary angiogram revealed a tight and isolated stenosis of the mid right coronary artery (top).

Coronary angioplasty was undertaken following the usual procedure (middle), during which multiple spasms were observed in the proximal and mid segments of the right coronary artery. The patient only felt moderate chest pain, and a modest ST segment elevation in the inferior leads was observed. Fortunately the spasm was successfully treated by intracoronary vasodilators (nitrates and verapamil).

The procedure was completed with two new inflations with a stent-like result (bottom); no immediate complications or long term restenosis occurred.

Though coronary artery spasm has been reported in 1–5% of balloon angioplasty procedures, it usually occurs at the site of the treated lesions or in the distal vessel. The multiple spasms in the proximal and mid epicardial artery observed in our patient are unusual, and probably resulted from irritation of the artery by the angioplasty equipment.

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