A comparison of inhaled nitric oxide with intravenous vasodilators in the assessment of pulmonary haemodynamics prior to cardiac transplantation

Abstract

Objectives. Elevated pulmonary vascular resistance and transpulmonary gradient are predictors of increased perioperative mortality in patients undergoing orthotopic heart transplantation. Sodium nitroprusside and prostacyclin PGI₂ are routinely used to assess the reversibility of pulmonary vascular resistance and transpulmonary gradient in heart transplant candidates, but their use is limited by their systemic vasodilatory effect. The aim of this study was to evaluate the systemic and pulmonary haemodynamic effects of low concentration (10 and 20 parts per million) inhaled nitric oxide in patients with severe heart failure with elevated transpulmonary gradient and pulmonary vascular resistance undergoing assessment for cardiac transplantation, and to compare the haemodynamic effects of inhaled nitric oxide with those of sodium nitroprusside and prostacyclin PGI₂.

Method. In 10 consecutive patients with elevated transpulmonary gradient (16 ± 2 mmHg) and pulmonary vascular resistance (3.6 ± 0.3 Wood units (WU)) nitric oxide (10 and 20 parts per million in 23% inspired oxygen (O₂) via a tight fitting face-mask) and increasing doses of intravenous sodium nitroprusside and prostacyclin were administered in a random, single-blinded fashion.

Results. Inhalation of nitric oxide (10 ppm) reduced the transpulmonary gradient (-7 ± 2 mmHg; P < 0.01) and pulmonary vascular resistance (-1.8 ± 0.4 WU; P < 0.001) but did not affect the systemic vascular resistance (-0.3 ± 1 WU) or mean systemic arterial pressure (-1.3 ± 5 mmHg). Sodium nitroprusside and prostacyclin reduced the transpulmonary gradient (-4.5 ± 2 mmHg; P < 0.01 and -3.6 ± 2 mmHg; P < 0.05), pulmonary vascular resistance (-1.5 ± 0.4 WU; P < 0.001 and -1.3 ± 0.4 WU; P < 0.01), systemic vascular resistance (-7 ± 2 WU; P < 0.01 and -7.2 ± 2 WU; P < 0.01) and mean systemic arterial pressure (-15 ± 5 mmHg; P < 0.01 and -18 ± 4 mmHg; P < 0.01).

Conclusion. Low-concentration inhaled nitric oxide is as effective as sodium nitroprusside and prostacyclin in reducing transpulmonary gradient and pulmonary vascular resistance, and is highly pulmonary vasoselective.

Key words Heart failure · Heart transplantation · Pulmonary hypertension · Nitric oxide
Introduction

An elevated pulmonary vascular resistance (PVR) or transpulmonary pressure gradient (TPG) in patients with heart failure is associated with an increased risk of perioperative and late death following orthotopic heart transplantation [4, 8]. There is no "cut off" value for PVR above which the risk of death increases sharply, but it is a continuous risk factor for premature death following transplantation [10]. The measurement of pulmonary haemodynamics is now a routine part of the assessment of potential cardiac transplant recipients. When the PVR and TPG are elevated, pharmacological manipulation of pulmonary haemodynamics using vasodilators is employed to determine whether the abnormalities of the pulmonary vascular bed are reversible or "fixed". Lack of response to vasodilators has been shown to identify a group of patients at high risk of death following orthotopic heart transplantation [3]. In addition, the determination of response to vasodilator therapy may be of use in the postoperative management of transplant patients [3, 12]. Vasodilator agents in common use include sodium nitroprusside and prostacyclin, but their main disadvantage is that they cause systemic vasodilation and hypotension. The "ideal" pulmonary vasodilator should be specific to the pulmonary vasculatory bed with no systemic effect. Inhaled nitric oxide (NO) has been shown to act as a selective pulmonary vasodilator without systemic effects at doses of 40–80 parts per million (ppm) in patients with both primary and secondary pulmonary hypertension [6, 13, 15], and at doses of 20–80 ppm in 12 patients assessed for cardiac transplantation and with elevated PVR and TPG [9]. The aim of this study was to evaluate the effects of low-dose inhaled NO (10 and 20 ppm) on pulmonary and systemic haemodynamics in potential heart transplant recipients with reversible pulmonary haemodynamics and to compare its effects with those of intravenous sodium nitroprusside and prostacyclin.

Patients and methods

The study was approved by the Ethical Committee of South Birmingham Health Authority. Ten consecutive patients (all male) (mean age 48 years; range 22–62 years) in end-stage heart failure undergoing right heart catheterization as part of their assessment for heart transplantation were studied after obtaining informed consent. Only the patients with PVR more than 2 Wood units were included in the study. The patient details are shown in Table 1. Vasodilator drugs were withheld for at least 12 h before the study and patients in atrial fibrillation were excluded. A thermodilution flotation catheter (Baxter Healthcare Corp., Santa Ana, Calif. USA) was inserted via the right subclavian vein and positioned in the pulmonary artery (Baxter Healthcare Corp., Santa Ana, Calif. USA) was inserted via the right subclavian vein and positioned in the pulmonary artery under fluoroscopy. Systemic arterial pressure was monitored continuously via a radial arterial cannula, which was also used for arterial blood gas sampling. Baseline pulmonary (at end expiration) and systemic haemodynamics were measured 30 min after catheter placement and after a 20-min period of haemodynamic stability (two consecutive measurements varying by less than 10%).

Following the acquisition of baseline measurements with the patient breathing room air (Table 1), the effects of NO were evaluated. Medical air and oxygen were mixed to give a final inspired oxygen concentration of 23% at a flow rate of 10 l/min. The gas was administered via a tight-fitting face mask using a non-rebreathing circuit. Three groups of pulmonary and systemic haemodynamic data were recorded for each patient in a random single blinded order: (1) 23% oxygen only (control), (2) 23% oxygen with NO at 10 parts per million (ppm) (NO 10) and (3) 23% oxygen with nitric oxide at 20 ppm (NO 20). The haemodynamic changes in group 1 were evaluated in order to differentiate the changes caused by NO from those caused by increasing the fractional inspired oxygen (FiO2) to 23%. Each concentration of gas was inspired for 10 min before acquiring data and a minimum period of 10 min for return to baseline haemodynamics (within 10%) was allowed before commencing the subsequent inhalation.

The second part of the study was to compare the haemodynamic effects of intravenous sodium nitroprusside (Nipride; P. Hoffman LaRoche Ltd., Basel, Switzerland) and prostacyclin PG12 (Flolan: Wellcome Ltd., London, United Kingdom) with those of inhaled NO (BOC special gases, Guildford, Surrey, UK). The intravenous agents were administered in random order and each drug was administered at two doses: 10 μg kg–1 min–1 for sodium nitroprusside (SNP10), 5 μg kg–1 min–1 for prostacyclin (PGI5) and the maximum tolerated dose for each (SNPMax, PGIMax), compatible with a systolic arterial blood pressure of 80 mmHg or more. The investigator recording the data was blinded to the agent administered. Haemodynamic measurements were performed after 10 min of infusion of each drug at each dose and a minimum of 30 min was allowed after each drug for the return of baseline haemodynamics (within 10%).

Nitric oxide delivery

Prior to using inhaled NO, a clinical trial certificate was obtained from the Medicines Control Agency. Nitric oxide 1000 ppm in nitrogen was mixed with a fresh gas flow of oxygen-enriched air (FiO2 23%) and delivered (10 l min–1) to the proximal end of a Magill anesthetic breathing system (Intersurgical, Berkshire, England). Nitric oxide (100 and 200 ml min–1) was added to the circuit via a "T" piece, thus providing fractional inspired concentrations (FiNO) of 10 and 20 ppm, respectively. A 2 l reservoir bag was used on the Magill attachment to ensure the adequate mixing of gases. A gas flow of 10 l min–1 was used to simplify calculations and to exceed the

Table 1 Patient characteristics and baseline pulmonary haemodynamics. (DCM dilated cardiomyopathy, ICM ischaemic cardiomyopathy, PVR pulmonary vascular resistance, TPG transpulmonary gradient.) All the patients were on maximal medical therapy for heart failure including diuretics and ACE-inhibitors (except patient #8 who was unable to tolerate ACE-inhibitors)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>PVR (Wood units)</th>
<th>TPG (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>58</td>
<td>ICM</td>
<td>3.6</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>48</td>
<td>DCM</td>
<td>3.7</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>45</td>
<td>ICM</td>
<td>2.1</td>
<td>8</td>
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<tr>
<td>4</td>
<td>M</td>
<td>47</td>
<td>ICM</td>
<td>3.3</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>48</td>
<td>ICM</td>
<td>3.8</td>
<td>22</td>
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<tr>
<td>6</td>
<td>M</td>
<td>62</td>
<td>ICM</td>
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<td>8</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>62</td>
<td>ICM</td>
<td>4.8</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>22</td>
<td>DCM</td>
<td>3.0</td>
<td>13</td>
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<tr>
<td>9</td>
<td>M</td>
<td>45</td>
<td>ICM</td>
<td>3.4</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>50</td>
<td>ICM</td>
<td>4.2</td>
<td>25</td>
</tr>
</tbody>
</table>
Variables measured

The following variables were measured: right atrial pressure, mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), mean systemic arterial pressure (MAP), cardiac output (CO), heart rate (HR), arterial and mixed venous blood gases as methaemoglobin. The following variables were derived: transpulmonary pressure gradient (TPG) (MPAP - PCWP), pulmonary vascular resistance (PVR) (TPG/CO), systemic vascular resistance (SVR) ((MAP - right atrial pressure)/CO). The PVR/SVR ratio, a measure of pulmonary vasoselectivity, was also calculated for each drug. Arterial and mixed venous oxygen saturations (SaO2 and SvO2) and arterial oxygen tension (PaO2) were measured for baseline and for NO inhalation (ABL 300, Radiometer, Copenhagen, Denmark). The intrapulmonary shunt fraction was calculated using standard formulae. Methaemoglobin was measured as a percentage of the total haemoglobin in the blood using a CO-oxymeter (OSM3, Radiometer, Copenhagen, Denmark).

Statistical analysis

Each variable was calculated as a mean of three consecutive measurements. The data are presented as mean and standard error of mean (SEM). Comparison was made by analysis of variance for repeated measurements followed by paired t-tests with Bonferroni correction. A significance level of 5% was used in the analysis.

Results

Effects of nitric oxide

The pulmonary haemodynamic effects of inhaled NO are illustrated in Fig. 1. All the patients tolerated both doses of NO with no side effects. There were no significant changes in pulmonary or systemic haemodynamics with an FiO2 of 23% (control) compared to baseline, although the PaO2 increased significantly from baseline (8.8 ± 0.4 kPa) to control (10.1 ± 0.4 kPa), P < 0.05.

The inhalation of NO at 10 ppm caused a significant decrease in PVR (−1.8 ± 0.4 Wood units; P < 0.001) and TPG (−4.5 ± 2 mmHg; P < 0.01). The changes in MPAP and PCWP with NO did not achieve statistical significance but were constant in direction, producing a highly significant fall in TPG. There was no correlation between the changes in PVR and PCWP (r = −0.07; P = ns) and between the

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Fig. 1 (Co cardiac output, HR heart rate, MPAP mean pulmonary arterial pressure, PCWP pulmonary capillary wedge pressure, PVR pulmonary vascular resistance, TPG transpulmonary pressure gradient). Data are expressed as mean ± standard error of mean. Statistical significance (*) is shown for inhalation of nitric oxide (NO) at 10 and 20 parts per million and 23% oxygen only (control) versus the basal status. ** = P < 0.01; *** = P < 0.001; ns = not significant.
Table 2 Effects on nitric oxide, sodium nitroprusside and PGI2 on pulmonary and systemic haemodynamics. (CO cardiac output, HR heart rate, MAP mean arterial pressure, MPAP mean pulmonary artery pressure, PCWP pulmonary capillary wedge pressure, PGI2,5 PGI2 at 5 ng/kg/min, PGI2 MAX PGI2 at maximal tolerated dose, PVR pulmonary vascular resistance, SNP 10 sodium nitroprusside at 10 mcg/kg/min, SNP MAX sodium nitroprusside at maximal tolerated dose, SVR systemic vascular resistance, TPG transpulmonary gradient, 10 ppm 10 parts per million).

<table>
<thead>
<tr>
<th>MAP (mmHg)</th>
<th>NO (10 ppm)</th>
<th>SNP 10</th>
<th>SNP MAX</th>
<th>PGI2,5</th>
<th>PGI2 MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPA (mmHg)</td>
<td>45±3</td>
<td>40±3</td>
<td>28±2**</td>
<td>24±2**</td>
<td>35±4*</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>29±2</td>
<td>32±3</td>
<td>16±2**</td>
<td>11±4**</td>
<td>22±3</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>3.6±0.3</td>
<td>1.8±0.2**</td>
<td>2.1±0.3***</td>
<td>1.9±0.4***</td>
<td>2.3±0.3**</td>
</tr>
<tr>
<td>SVR (Wood units)</td>
<td>19±2</td>
<td>19±1</td>
<td>12±2**</td>
<td>8±1***</td>
<td>12±1**</td>
</tr>
<tr>
<td>PVR/SVR Ratio</td>
<td>0.195±0.021</td>
<td>0.100±0.002**</td>
<td>0.175±0.014</td>
<td>0.212±0.035</td>
<td>0.205±0.038</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.3±0.3</td>
<td>4.6±0.2</td>
<td>5.5±0.5*</td>
<td>6.9±0.6***</td>
<td>5.5±0.4**</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>94±4</td>
<td>96±2</td>
<td>79±5**</td>
<td>64±3***</td>
<td>76±4**</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>87±5</td>
<td>89±5</td>
<td>88±5</td>
<td>94±5</td>
<td>85±5</td>
</tr>
</tbody>
</table>

*=P<0.05, **=P<0.01, ***=P<0.001

Table 2: Effects on nitric oxide, sodium nitroprusside and PGI2 on pulmonary and systemic haemodynamics. (CO cardiac output, HR heart rate, MAP mean arterial pressure, MPAP mean pulmonary artery pressure, PCWP pulmonary capillary wedge pressure, PGI2,5 PGI2 at 5 ng/kg/min, PGI2 MAX PGI2 at maximal tolerated dose, PVR pulmonary vascular resistance, SNP 10 sodium nitroprusside at 10 mcg/kg/min, SNP MAX sodium nitroprusside at maximal tolerated dose, SVR systemic vascular resistance, TPG transpulmonary gradient, 10 ppm 10 parts per million).

Discussion

Although our study is similar to the one by Kieler-Jensen et al. [9], our aim was to confirm their findings obtained on a small number of patients and to test whether even lower doses of NO were as effective as the ones used by these authors.

We have demonstrated that inhaled NO is as effective as conventional intravenous vasodilators in reducing PVR and TPG in patients with severe heart failure. These effects were not significantly different in magnitude at concentration of 10 and 20 ppm. All the patients in this study were found to have "reversible" pulmonary vasoconstriction with each agent studied, so that no conclusions can be drawn on whether inhaled NO has a role in cases in which the pulmonary vasoconstriction appears "fixed" on challenge with conventional intravenous vasodilators. In contrast to both sodium nitroprusside and prostacyclin, the pulmonary vasodilatation seen with inhaled NO was obtained without any change in systemic haemodynamics. Both intravenous agents caused profound arterial hypotension and, in the case of prostacyclin in particular, patient tolerance was poor.

There were marked differences between NO and the conventional intravenous vasodilators in the way in which the improvements in pulmonary haemodynamics were achieved. No change in CO occurred during NO adminis-
Wood units

PVR

mmHg

TPG

Wood units

SVR

mmHg

MAP

Fig. 2 (MAP mean systemic arterial pressure, PVR pulmonary vascular resistance, SVR systemic vascular resistance, TRG transpulmonary gradient). Data is expressed as changes of mean values from basal status ± standard error of mean (NO10 nitric oxide 10 ppm, SNP10 sodium nitroprusside 10 μg/kg·min⁻¹, SNPMax sodium nitroprusside at maximal tolerated dose, PGI5 prostacyclin at 5 ng/kg·min⁻¹, PGI5Max prostacyclin at maximal tolerated dose.) Statistical significance is shown versus basal status × P<0.05, ××: P<0.01, ×××: P<0.001. ψ=P<0.05 versus basal status, for 6 patients, ϕ=P<0.05 versus basal status, for 9 patients.

and PCWP so that the changes in TPG tended to be smaller. In addition, there were large increases in CO.

The tendency of inhaled NO to produce increases in the PCWP in patients with left ventricular function has been observed before [9, 11] and the mechanism remains unclear. A negative inotropic action upon the left ventricle is unlikely, in view of the immediate binding of NO by haemoglobin [14]. A speculative explanation is the pulmonary vasodilatory effect of NO in the presence of impaired left ventricular function. This could lead to an increased venous return to the failing left ventricle and an increase in its volume. Although this normally leads to an increase in ejection fraction and stroke volume in normal ventricles, in the patients studied left ventricular function was very depressed and working on the flat portion of the Starling relation [11].

The absence of any increase in CO with NO is perhaps the most significant difference between this agent and the...
intravenous vasodilators. An increase in CO with intravenous vasodilators is probably a result of the improved loading conditions and a reflex increase in sympathetic activity. The increased output may, in itself, result in pulmonary vasodilatation, both directly as a result of vessel distension and indirectly perhaps by causing NO release as a result of shear stress. A major advantage of NO in the assessment of pulmonary haemodynamics may be its capacity to act upon the pulmonary vasculature without causing changes in CO, so that a true measure of the capacity of the pulmonary vascular bed to dilate is obtained.

Inhaled NO is a selective pulmonary vasodilator because its rapid inactivation by haemoglobin, to form methaemoglobin, prevents systemic effects [1, 2, 14]. Its use in reducing PVR without any systemic hypotension has been reported in a number of animal studies and clinical studies of patients with pulmonary hypertension [6, 7, 13]. The efficacy of NO in reducing PVR has been demonstrated in both primary and secondary (due to mitral valve disease) pulmonary hypertension [6, 13, 15]. In these patients inhaled NO caused significant reductions in MPAP with little or no change in PCWP or CO. A recent report also examined the use of inhaled NO in the assessment of pulmonary haemodynamics prior to cardiac transplantation [9]. In this study similar effects on pulmonary haemodynamics to those reported above were demonstrated with no change in MPAP or CO but a significant increase in PCWP.

A problem often not appreciated with conventional vasodilators is that dilating poorly ventilated areas of lung and increasing the CO leads to increased shunting and reduced SaO₂ [9]. We did not measure shunt fraction with the intravenous agents in our study but we did note that there was no change with NO at 10 and 20 ppm, possibly because only those areas of the lung which are ventilated are vasodilated as a result of exposure to NO.

The low doses of inhaled NO employed in this study contrast with previous work in which the usual concentrations used have been 40–80 ppm. Nitric oxide leads to the formation of methaemoglobin which accumulates during its inhalation [6]. This reduces the oxygen carrying capacity of the blood so that methaemoglobin concentrations must be monitored. In addition, the inhalation of high concentration NO (80 ppm) leads to the formation of potentially toxic concentrations of NO₂ and has been shown to increase shunt fraction and decrease PaO₂ [9]. A low dose of NO will minimise these potentially adverse effects, and it appears that 10 ppm results in clinically useful effects.

The use of sodium nitroprusside to differentiate fixed from reversible pulmonary hypertension in patients undergoing assessment for cardiac transplantation was suggested over 20 years ago [8]. Its utility in identifying groups of patients at high and low risk of death and right ventricular failure after transplantation has been demonstrated [3]. There is some evidence that prostaglandin E₁ may be able to demonstrate reversibility in cases resistant to sodium nitroprusside [5]. We suggest that inhaled NO may be a safer, better tolerated pulmonary selective vasodilator without potentially confusing effects on pulmonary haemodynamics as a result of increases in CO. Much larger studies are required to determine whether this agent can be used to identify those patients at high and low risk of perioperative death and right ventricular failure after transplantation and to determine its utility in patients with apparently fixed pulmonary hypertension on challenge with intravenous vasodilators.

**Acknowledgements**

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**References**


Discussion

**Dr. S. Large (Cambridge, UK): Dr. Pagano**, I really enjoyed your paper a great deal. I thought it was very helpful seeing what you might argue as being the deleterious effects of agents such as sodium nitroprusside. I was a little disappointed to see that you hadn’t looked at an FIO₂ of one. Did you play around with oxygen, the oxygen tension, inhaled oxygen tension in your comparison?

**Dr. Pagano**: Thank you Mr. Large. From our previous experience, breathing 100% oxygen does not result in a significant reduction in pulmonary vascular resistance in patients with end-stage heart failure and adverse pulmonary haemodynamics, and therefore we did not explore the effects of this agent in our study.