Comparison of Inhaled Nitric Oxide and Inhaled Aerosolized Prostacyclin in the Evaluation of Heart Transplant Candidates With Elevated Pulmonary Vascular Resistance

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Comparison of Inhaled Nitric Oxide and Inhaled Aerosolized Prostacyclin in the Evaluation of Heart Transplant Candidates With Elevated Pulmonary Vascular Resistance*

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Study objective: Elevated pulmonary vascular resistance is a risk factor in heart transplantation and reversibility of high pulmonary vascular resistance is evaluated preoperatively in potential recipients using IV vasodilators or inhaled nitric oxide. Prostacyclin is a potent vasodilator, which when inhaled, has selective pulmonary vasodilatory properties. The aim of this study was to compare the central hemodynamic effects of inhaled prostacyclin with those of inhaled nitric oxide in heart transplant candidates.

Design: A pharmacodynamic comparative study.

Setting: Cardiothoracic ICU or laboratory for diagnostic heart catheterization at a university hospital.

Patients: Ten heart transplant candidates with elevated pulmonary vascular resistance (>200 dynes·s·cm⁻² and/or a transpulmonary pressure gradient >10 mm Hg) were included in the study.

Interventions: Nitric oxide (40 ppm) and aerosolized prostacyclin (10 µg/mL) were administered by inhalation in two subsequent 10-min periods. Hemodynamic measurements preceded and followed inhalation of each agent.

Measurements and results: Both inhaled nitric oxide and inhaled prostacyclin reduced mean pulmonary artery pressure (−7% vs −7%), pulmonary vascular resistance (−43% vs −49%), and the transpulmonary gradient (−44% vs −38%). With inhaled prostacyclin, an 11% increase in cardiac output was observed. Other hemodynamic variables, including the systemic BP, remained unaffected by each of the agents.

Conclusions: Inhaled prostacyclin induces a selective pulmonary vasodilation that is comparable to the effect of inhaled nitric oxide. Major advantages with inhaled prostacyclin are its lack of toxic reactions and easy administration as compared with the potentially toxic nitric oxide requiring more complicated delivery systems.

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Key words: aerosolized prostacyclin; heart transplantation; inhalation; nitric oxide; pulmonary hypertension

Abbreviations: CO=cardiac output; CVP=central venous pressure; HR=heart rate; LV=left ventricle; MAP=mean arterial pressure; MPAP=mean pulmonary artery pressure; NO=nitric oxide; NO₂=nitrogen dioxide; PCWP=pulmonary capillary wedge pressure; PGI₂=prostacyclin; PVR=pulmonary vascular resistance; SaO₂=arterial oxygen saturation; SV=stroke volume; SvO₂=venous oxygen saturation; SVR=systemic vascular resistance; TPG=transpulmonary pressure gradient

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Elevated pulmonary vascular resistance (PVR) in heart transplant candidates increases the perioperative morbidity and mortality due to acute right ventricular failure of the graft after orthotopic heart transplantation.¹,² Potential recipients are evaluated by measurement of central hemodynamic variables and calculation of the transpulmonary pressure gradient (TPG) (mean pulmonary artery pressure [MPAP] minus pulmonary capillary wedge pressure [PCWP]) and PVR. The reversibility of an elevated PVR is usually determined by IV administration of vasodilators such as nitrates or prostaglandins.³ If the pulmonary hypertension is reversible, the patient can...
be considered as suitable for orthotopic heart transplantation and a vasodilator can be used perioperatively to prevent and treat right ventricular failure of the transplanted heart. Due to the shortage of donor organs, it is even more important to determine reversibility and hence avoid transplantation of lungs resulting in an efficient utilization of available grafts.

However, neither nitrates nor prosta-glandins exert a desirable selective pulmonary vasodilation when used IV but may instead induce systemic vasodilation with hypotension which, in turn, will jeopardize right ventricular perfusion. The biomediator nitric oxide (NO) has, when inhaled in concentrations of 5 to 80 ppm, selective pulmonary vasodilatory properties without effects on the systemic vasculature. A disadvantage with NO is that it is a highly toxic molecule and the production of methemoglobin and higher oxides of nitrogen is a major concern requiring specialized delivery systems and monitoring.

Prostacyclin (PGI₂) is another biomediator synthesized by the vascular endothelium. It is a potent vasodilator with no toxic effects and a half-life of 2 to 3 min. Inhaled PGI₂ has been shown to induce a dose-dependent selective pulmonary vasodilation after heart surgery and heart transplantation and to have beneficial effects on the pulmonary vasculature and oxygenation in patients with ARDS as well as other conditions associated with pulmonary hypertension.

The aim of the present study was to compare the pulmonary vasodilatory effects of inhaled PGI₂ with those of inhaled NO in heart transplant candidates with elevated PVR.

**Materials and Methods**

The study was performed at Sahlgrenska University Hospital, Göteborg, Sweden, and approved by the Human Ethics Committee of the Medical Faculty, University of Göteborg, Ten patients, 4 female and 6 male (24 to 59 years of age, mean 49 years) with elevated PVR (PVR >200 dyn·s·cm⁻¹ and/or TPG >10 mm Hg) were included after informed consent. The patients were scheduled for diagnostic right heart catheterization. The diagnoses were ischemic (n=5) or dilated (n=5) cardiomyopathy (Table 1).

Measurements of central hemodynamics were performed using a radial artery catheter and a pulmonary artery thermodilution catheter (Swan-Ganz model 131H; F; Edwards Laboratory, Santa Ana, Calif) inserted via the right jugular vein. The following variables were measured or calculated: cardiac output (CO) was measured in triplicate, heart rate (HR), stroke volume (SV), systolic, diastolic, and mean (MAP) arterial BPs, systolic, diastolic, and mean (MPAP) pulmonary arterial pressures, central venous pressure (CVP), PCWP, systemic vascular resistance (SVR) and PVR, and the TPG (MPAP-PCWP). The PVR/SVR ratio was also calculated for each drug. Arterial and mixed venous oxygen saturation (SaO₂ and SvO₂) were measured as well as PaO₂. The intrapulmonary shunt fraction and whole-body oxygen extraction were calculated using standard formulas.

<p>| Table 1—Patient Characteristics Prior to Inclusion* |
|-----------------------------------------|-----------|----------|---------|------|
| Patient/                        | Age,     | Diagnosis | PVR,    | TPG,    | LVEF   |</p>
<table>
<thead>
<tr>
<th>yr/Sex</th>
<th></th>
<th></th>
<th>dyne · s · cm⁻¹</th>
<th>mm Hg</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1/24/MPathological shunt</td>
<td>49</td>
<td>DCM</td>
<td>479</td>
<td>14</td>
<td>0.20</td>
</tr>
<tr>
<td>2/50/MPathological shunt</td>
<td>53</td>
<td>IHD</td>
<td>196</td>
<td>11</td>
<td>0.19</td>
</tr>
<tr>
<td>3/50/MPathological shunt</td>
<td>25</td>
<td>IHD</td>
<td>351</td>
<td>23</td>
<td>0.20</td>
</tr>
<tr>
<td>4/52/MPathological shunt</td>
<td>44</td>
<td>IHD</td>
<td>464</td>
<td>29</td>
<td>0.30</td>
</tr>
<tr>
<td>5/58/FPathological shunt</td>
<td>55</td>
<td>DCM</td>
<td>291</td>
<td>13</td>
<td>0.30</td>
</tr>
<tr>
<td>6/59/FPathological shunt</td>
<td>70</td>
<td>DCM</td>
<td>396</td>
<td>39</td>
<td>0.30</td>
</tr>
<tr>
<td>7/57/MPathological shunt</td>
<td>28</td>
<td>IHD</td>
<td>396</td>
<td>15</td>
<td>0.15</td>
</tr>
<tr>
<td>8/59/MPathological shunt</td>
<td>29</td>
<td>DCM</td>
<td>291</td>
<td>11</td>
<td>0.20</td>
</tr>
<tr>
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<td>29</td>
<td>DCM</td>
<td>769</td>
<td>25</td>
<td>0.18</td>
</tr>
<tr>
<td>10/24/FPathological shunt</td>
<td>29</td>
<td>DCM</td>
<td>267</td>
<td>8</td>
<td>0.20</td>
</tr>
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</table>

*DCM=dilated cardiomyopathy; IHD=ischemic heart disease; LVEF=left ventricular ejection fraction.

**Experimental Procedure**

The study was divided into four subsequent 10-min periods, each followed by hemodynamic measurements and sampling for arterial and mixed venous oxygen content. The experimental procedure started with a control period of spontaneous breathing at an inspiratory fraction of oxygen of 20% via a tightfitting face mask in a nonbreathing system. After baseline hemodynamic measurements, NO (40 ppm) was added to the system for 10 min followed by another 10-min control period. Aerosolized PGI₂ (Filon; Wellcome Laboratories; Beckenham, Kent, UK) was then administered for 10 min at a concentration of 10 μg/mL by inhalation through a mouthpiece, using a high-efficiency nebulizer (see below).

**NO Administration and Monitoring**

The delivery system for NO to the breathing gas consisted of two mass-flow-regulators controlling the flow of NO mixed in nitrogen (1,000 ppm; AGA Gas AB; Solna, Sweden) and an oxygen/air mixture, respectively. A soda¬lime-absorber placed close to the patient on the inspiratory limb was used for scavenging of nitrogen oxide (NO₂). NO₂ measurements with ultraviolet technique (Binos NO; Leybold-Horneus GmbH; Hanau, Germany) in breathing gas to the patient has shown NO₂ values well below 0.5 ppm at the NO and oxygen concentration used in the present study (40 ppm and 30%, respectively). The level of inhaled NO was monitored continuously using electrochemical fuel-cell-technique (City Technology; London, UK).

**Prostacyclin Administration**

The nebulizer used for inhalation of PGI₂ (Maxin MA-2; Clinova Medical AB; Malmö, Sweden) (Fig 1) is a high-efficiency nebulizer, 68% of the particles have a mean mass diameter <4 μm. The delivery rate is low output 0.2 to 0.3 mL/min, and the flow of aerosol with a driving pressure of 5 bar is 4.5 L/min. Lung deposition is 90% and lung retention is 50% according to the manufacturer. PGI₂ was prepared in a glycine buffer (0.18% glycine, 0.147% sodium chloride, pH 10.5) immediately before use to a concentration of 10 μg/mL. Each patient received 2 to 3 mL of PGI₂ solution (20 to 50 μg).

**Statistical Analysis**

Data are presented as mean ± SEM. Data were compared using a two-way analysis of variance for repeated measurements. The
Figure 1. Nebulizer (Maxin MA-2).

differential effect of PGI$_2$ as compared with NO were evaluated using the analysis of variance interaction analysis. A p value <0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics prior to inclusion are shown in Table 1. Mean values for central hemodynamic variables during control and during PGI$_2$ and NO inhalation are given in Table 2. No CO values were obtained for patient 7 due to a severe tricuspid valve insufficiency. Individual data on the effects of inhalation on MPAP, PCWP, TPG, and PVR are shown in Figure 2.

Effects of Inhaled NO 40 ppm on Central Hemodynamics (Table 2)

During inhalation of NO, PCWP increased (+21%) while MPAP decreased (-7%) as well as TPG (-42%), PVR (-43%), and PVR/SVR ratio.
(-44%). Inhaled NO caused no changes in HR, MAP, CVP, CO, SV, or SVR.

**Effects of Inhaled PGi2 on Central Hemodynamics (Table 2)**

During inhalation of PGi2, PCWP increased (+21%) while MPAP decreased (-7%) as well as TPG (-44%), PVR (-49%), and PVR/SVR ratio (-38%), while there were no changes in HR, MAP, CVP, SV, or SVR. Inhaled PGi2 induced an increase in CO (+11%).

**Oxygenation Parameters**

During inhalation of PGi2 or NO, no changes in SaO2, SvO2, oxygen extraction, or PaO2 were observed. The intrapulmonary shunt was significantly increased during PGi2 inhalation.

**DISCUSSION**

In the present study, we have compared the effects of inhaled aerosolized PGi2 (concentration in solution 10 µg/mL) with those of inhaled NO (40 ppm) on central hemodynamics in heart transplant candidates with congestive heart failure and elevated PVR. The main findings were that inhaled PGi2 induced a pulmonary vasodilation, with a decrease in PVR, MPAP, and TPG, comparable to that induced by inhaled NO. Furthermore, inhaled PGi2 caused no significant effect on SVR. It is not immediately obvious why inhaled PGi2, in contrast to inhaled NO, induced a slight (11%) but significant increase in CO. Previous *in vitro* studies have suggested that PGi2 may exert a mild positive inotropic effect which, however, has not been confirmed in patients. One could speculate whether the tendency of a PGi2-induced decrease in SVR reflected...
a minor “spill-over” of PGI₂ to the systemic circulation, in turn unloading the failing left ventricle (LV).

More patients are required to establish whether, in fact, such a spill-over effect of inhaled PGI₂ is real or not.

Evidence that inhalation of aerosolized PGI₂ may induce a selective pulmonary vasodilation was first provided by Welte et al.²⁰ in a canine model of pulmonary hypertension. Inhaled PGI₂ has also been shown to reduce pulmonary arterial pressure and improve oxygenation in both adults and infants with respiratory distress syndrome.¹⁹,²²,²⁹ We have recently described the effects of incremental concentrations of inhaled PGI₂ (2.5, 5, and 10 μg/mL) in patients with postoperatively elevated PVR after heart surgery or heart transplantation.¹⁷ In that study, inhaled PGI₂ induced a selective dose-dependent decrease in PVR and the TPG with no effects on systemic vasculature and with a maximal effect seen at an inhaled concentration of 10 μg/mL. The selective pulmonary vasodilatory effect of NO is well described in both animal and human studies.³,⁰,³¹ Gradually increased doses of inhaled NO (5 to 80 ppm) have been documented to decrease PVR in patients with chronic pulmonary hypertension, in cardiac surgical patients, after heart transplantation, and in patients supported with ventricular assist devices after heart surgery.¹⁰,¹¹,³²,³³ In a recent study, we evaluated the effects of incremental doses of inhaled NO (5, 10, 20, and 40 ppm) on PVR in heart transplant candidates with elevated PVR.⁸ We found that inhaled NO at a concentration of 20 ppm was the lowest mean dose to cause a maximal reduction in PVR, even though a few patients required 40 ppm.

The use of NO for evaluation of heart transplant candidates with pulmonary hypertension has been described previously not only by us⁸ but also by others.³⁴,³⁵ The decrease in PVR in those studies was associated with an increase in PCWP. The mechanism behind this NO-induced increase in PCWP in patients with left heart failure is unknown. It is probably not caused by an NO-induced negative inotropic effect as NO is most likely inactivated by hemoglobin before it reaches the LV and NO donors such as sodium nitroprusside or nitroglycerin do not exert a negative effect on myocardial contractility. We therefore hypothesized that inhaled NO causes a redistribution of blood from precapillary to postcapillary pulmonary capacitance vessels with a consequent increase in LV end-diastolic volume and filling pressure.⁸ This would have caused an increase in LV stroke volume in a normal LV but not in our patients with severely depressed LV function. A small increase in the capacity of postcapillary capacitance vessels and LV end-diastolic volume, induced by NO, might cause a large increase in PCWP due to the increased stiffness of the failing LV. This hypothesis is supported by the finding that NO induces a greater vasodilation of postcapillary compared with precapillary vessels in patients with ARDS and high PVR.³⁶ This hypothesis was further supported by a recent study of Hare et al.,³⁷ in which the effects of inhaled NO on LV filling pressure were studied in patients with LV failure receiving an LV assist device. When the pump delivered a fixed systemic flow, the selective reduction in PVR by NO increased left atrial pressure, i.e., inhaled NO increases LV filling pressure by increasing pulmonary venous volume. In the present study, an increase in LV filling pressure was seen, both for inhaled PGI₂ and inhaled NO, suggesting that the mechanism behind the decrease in PVR and TPG is probably the same for inhaled PGI₂ as for inhaled NO. In other words, one could speculate that both inhaled NO and inhaled PGI₂ act to a greater extent on the postcapillary compared with the precapillary portion of the pulmonary vascular bed.

In this study, both PGI₂ and NO inhalation produced a selective pulmonary vasodilation as illustrated by the marked decrease in the PVR/SVR ratio. Pulmonary vasodilation by IV vasodilators is accompanied by a corresponding decrease in SVR, with no decrease in the PVR/SVR ratio and a decrease in arterial pressure.⁸ This systemic hypotension limits the use of IV nonspecific vasodilators in the evaluation of heart failure patients with elevated PVR, especially in those with ischemic heart disease, and also in the postoperative treatment of these patients after heart transplantation.⁵,¹⁷,³³ In contrast, inhalation of PGI₂ and NO produces a rapid and reversible pulmonary vasodilation without concomitant systemic hypotension.⁵,¹⁷,³³ In recent studies, the pulmonary hemodynamic effects of inhaled NO have been compared with those of inhaled aerosolized PGI₂ in patients with ARDS²⁵ and severe pulmonary hypertension.³⁹ Walrath et al.²⁵ demonstrated in 16 patients with ARDS that inhaled NO and inhaled PGI₂ reduce MPAP, PVR, and intrapulmonary shunt to the same extent. In six patients with severe primary or secondary pulmonary hypertension, inhaled PGI₂ was even more effective than inhaled NO in the reduction of MPAP or PVR as demonstrated by Olszewski.³⁹ One can thus conclude from the data of those reports and the present study that the efficacy of inhaled PGI₂ to improve pulmonary hemodynamics in patients with high PVR, irrespective of the underlying disease, is at least comparable to that seen with inhaled NO.

In the present study, it was observed that inhalation of PGI₂ induced a slight increased pulmonary
shunt that could be explained by an increase in lung water in these patients with severe cardiac failure, because of the increase in PCWP, in combination with a prolonged period in the supine position. Indeed, some patients also developed clinical signs of pulmonary congestion during NO and PGI$_2$ inhalation that was associated with the development of pronounced V waves on the PCWP tracing.

Inhaled PGI$_2$ has no toxic effects or toxic metabolites and requires only standard systems for nebulizing therapy. Possible side effects of PGI$_2$ are profound hypotension and tachycardia induced by an overdose of the agent. Systemic effects of PGI$_2$ inhalation have been reported only with inhaled concentrations of PGI$_2$ 100 times greater than those reported in the present study. Inhibition of platelet aggregation is another possible side effect of PGI$_2$ inhalation that may increase the risk of intraoperative and postoperative bleeding. However, no effects on platelet aggregation were demonstrated during prolonged (8 h) PGI$_2$ inhalation in an animal setting, but should be studied also in humans. A major concern has also been the effect of the highly alkaline glycine buffer PGI$_2$ solution on global biochemical and cellular composition of the alveolar epithelial lining fluid. This was investigated in an experimental lamb model in which inhaled PGI$_2$ for 8 h did not cause signs of acute pulmonary toxicity.

In conclusion, a brief period of inhaled PGI$_2$ provides a simple, pulmonary selective test of the reversibility of an elevated PVR in heart transplant candidates, which is comparable to the effects of inhaled NO with respect to both pulmonary vascular and systemic effects. The advantages of inhaled PGI$_2$ in comparison to NO is its atoxicity and simple technology for its administration.

REFERENCES


CHEST / 114 / 3 / SEPTEMBER, 1998 785
Welte vasoconstriction pulmonary vasoconstriction intravenous clin conference.


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