Hemodynamic effects of inhaled aerosolized iloprost and inhaled nitric oxide in heart transplant candidates with elevated pulmonary vascular resistance

Armin Sablotzki a, *, Thomas Hentschel a, Ekkehard Gruenig b, Susann Schubert a, Ivar Friedrich c, Jörg Mühling d, Marius G. Dehne d, Elke Czeslick a

a Clinic of Anesthesiology and Intensive Care Medicine, Martin-Luther-University Halle/Wittenberg, Ernst-Grube-Strasse 40, 06120 Halle/Saale, Germany
b Clinic of Internal Medicine III, University of Heidelberg, 69117 Heidelberg, Germany
c Clinic of Cardiothoracic Surgery, Martin-Luther-University Halle/Wittenberg, 06120 Halle/Saale, Germany
d Department of Anaesthesiology and Intensive Care Medicine, University of Giessen, 35392 Giessen, Germany

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Abstract

Objective: An elevated pulmonary vascular resistance (PVR) is described as a predictor of postoperative right heart failure and increased mortality in patients undergoing orthotopic heart transplantation. The use of intravenous vasodilators is limited by their systemic effects. We evaluated the pulmonary and systemic hemodynamic effects of inhaled nitric oxide (NO) and inhaled aerosolized iloprost (IP) in heart transplant candidates with elevated PVR.

Methods: Fourteen male heart transplant candidates due to dilative or ischemic cardiomyopathy with elevated PVR (≥180 dyn s cm⁻²) were included in the study. Increasing concentrations of NO (5, 10 and 30 ppm) and 50 µg aerosolized IP were administered by inhalation. Hemodynamic measurements preceded and followed administration of each agent.

Results: Inhalation of IP, 10, and 30 ppm NO reduced PVR and mean pulmonary artery pressure (MPAP), but did not affect blood pressure or systemic vascular resistance. Comparing the effectiveness of 10 ppm NO and IP, we found a significant higher reduction of MPAP in patients treated with IP. An increase of cardiac index and stroke index could only be shown with IP inhalation.

Conclusions: Inhaled iloprost induces pulmonary vasodilation which is significantly greater than the effects of 10 and 30 ppm NO. The results of our study show, that inhaled iloprost induces a reliable hemodynamic response in the evaluation of heart transplant candidates. Further advantages of iloprost inhalation are the lack of adverse reactions and toxic side effects and an easier administration. Due to this facts we recommend iloprost as a routine screening drug for vascular reactivity in HTx-candidates. Based on our results it would be of great interest to investigate the role of iloprost in management of postoperative right heart insufficiency following cardiac transplantation.

Keywords: Nitric oxide; Iloprost; Heart transplantation; Pulmonary hypertension

1. Introduction

In patients with chronic left ventricular failure pulmonary vascular resistance (PVR) is frequently elevated as a result of dysregulation of vascular smooth muscle tone and structural remodeling. In more than 50% of patients, waiting for a heart transplantation, an elevated PVR (>2.2 Wood-Units) is present. The resulting pulmonary hypertension led to a significant increase in perioperative mortality following orthotopic heart transplantation due to acute right ventricular failure of the graft [1,2]. The measurements of pulmonary hemodynamics is a routine procedure in the assessment of potential transplantation recipients. In case of elevated PVR, drugs such as nitrates, sodium nitroprusside, or prostacyclin are used to determine whether the abnormalities of the pulmonary vascular bed are reversible or not. The information about the response to vasodilator therapy is of great interest for the postoperative management of right heart failure [3].

The main disadvantage and therapeutic limitation of intravenous vasodilators is the systemic vasodilation and hypotension [4]. Inhaled nitric oxide and prostacyclin (PGI₂) have been shown to act as selective pulmonary vasodilators without systemic effects in patients with primary and secondary pulmonary hypertension as well [5–8]. Unfortunately, nitric oxide (NO) is a toxic molecule and
the production of methemoglobin and higher oxides of nitrogen requires specialized delivery systems and monitoring, especially during long-term treatment [9]. But even short periods of NO-administration may be associated with an increase in left ventricular filling pressure in patients with heart failure due to an increased pulmonary venous return to a poorly compliant left ventricle, resulting in an acute pulmonary edema [10]. Because of its short half-life, NO has to be administered continuously, and even brief interruptions may cause a dangerous rebound of pulmonary hypertension [11].

Weston and colleagues reported about benefits of prostacyclin-inhalation in heart transplant candidates with nitroprusside-resistant pulmonary artery hypertension; further advantages are the lack of toxic reactions and easy administration [12]. On the other hand, Haraldsson found no improved effects on hemodynamic variables, comparing inhaled prostacyclin with inhaled NO in the evaluation of heart transplantation (HTx)-candidates [8].

Olschewski and coworkers described the use of aerosolized iloprost, a carbacyclin analog of PGI₂, for severe pulmonary hypertension [13]. Iloprost has a plasma half life of 20–30 min, when inhaled it seems to induce pulmonary vasodilation that persists for about 2–4 h. In contrast to NO, inhaled iloprost may also exert systemic circulatory effects, as the molecule will not be rapidly inactivated in the pulmonary vascular bed and ‘spill over’ in the systemic circulation [8]. In patients with primary pulmonary hypertension iloprost was more potent than inhaled NO [14].

Currently, there are only case reports about the use of iloprost in patients with secondary pulmonary hypertension caused by chronic cardiac failure [15,16]. The aim of the present study was to compare the hemodynamic effects of inhaled NO and inhaled aerosolized iloprost in heart transplant candidates with elevated pulmonary hypertension.

2. Materials and methods

The study protocol was approved by the Human Ethics Committee of the Medical Faculty, University of Halle/Wittenberg. Fourteen male patients with elevated PVR (266.7 ± 78 dyn s cm⁻⁵) scheduled for diagnostic right heart catheterization were included after informed consent. The diagnoses were ischemic (n = 6) or dilated (n = 8) cardiomyopathy. Patients received their usual regimen of oral medication in the morning, no additional sedation were administered during insertion of lines or the study procedure.

Measurement of central hemodynamics were performed using a radial artery catheter and a pulmonary artery catheter (Edwards model 93A-434-7.5F; Baxter Healthcare Corp., Irvine, CA, USA), inserted via the left jugular vein. The following variables were measured or calculated: systolic, diastolic, and mean arterial blood pressure (MAP), heart rate, systolic, diastolic, and mean pulmonary artery pressure (MPAP), central venous pressure, pulmonal capillary wedge pressure (PCWP), stroke volume, systemic (SVR) and PVR. Cardiac output was measured, cardiac index (CI), pulmonary and systemic vascular resistance indices, and stroke index (SI) were calculated. Arterial and mixed venous blood samples were obtained simultaneously for determination of oxygen saturation (arterial saturation, SaO₂, mixed venous saturation, SvO₂), pCO₂, pO₂, lactate, hemoglobin,
methemoglobin, and base excess. All parameters were determined at baseline and at the end of each evaluation period. Triplicate measurements were averaged for each reported cardiac output.

Prior to the acquisition of baseline measurements and during the whole study period the patients were breathing medical air and oxygen in an inspiratory concentration of 25% via a tight-fitting face mask using a non-rebreathing circuit (Ventilator EVITA-IV; Drägerwerk, Lübeck, Germany). Nitric oxide (1000 ppm in nitrogen; Messer-Griesheim, Frankfurt, Germany) was administered via a ‘T-piece’ in an inspiration-triggered modus to the inspiratory limb of the breathing device (Siemens-Nebulizer 945; Siemens, München, Germany). The NO concentration was measured using a chemoluminometer (NO-domo; Drägerwerk, Lübeck, Germany) (Fig. 1).

After inhaling NO in concentrations of 5, 10 and 30 ppm, a complete evaluation of hemodynamics and blood gases was performed. Thereafter, NO was discontinued and after 20 min of washout new basic hemodynamics were obtained before the inhalation of iloprost (Ilomedin®; Schering AG, Berlin, Germany) was started. A total of 50 μg of iloprost were diluted in 3 ml of isotone saline solution and nebulized (Cirrus™ 2505, Intersurgical, UK) in the same breathing device described above for 15 min. Another hemodynamic measurement followed 5 min after the iloprost inhalation.

2.1. Statistics

Statistical analysis was made by an independent bureau of statistics (MoRe.Data, Giessen, Germany). The data are presented as mean values and standard deviation (SD). Comparison of data was made by non-parametric Friedman-test, followed by Wilcoxon–Wilcoxon-test. A P-value < 0.05 was considered to indicate statistical significance [17].

3. Results

We studied 14 adult male patients. The mean age was 52.8 ± 5.8 years, the body surface area was 2.02 ± 0.16 m². All treated patients tolerated all doses of NO and iloprost without side effects, the peak concentration of methemoglobin in arterial blood was 0.7%.

The hemodynamic effects of inhaled NO and iloprost are illustrated in Figs. 2 and 3. There were no significant effects
of both NO and iloprost on mean arterial blood pressure and systemic vascular resistance compared to the baseline. Iloprost-inhalation resulted in a greater decrease in MPAP than NO. The resultant values with iloprost (24.8 ± 8.5 mmHg) were significantly lower than the 27.1 ± 8 mmHg associated with NO ($P < 0.01$). The PVR was significantly

Fig. 3. Influence of inhaled NO and iloprost on PCWP, CI, SI, and TPG, $n = 14$. Data are expressed as mean ± SD. * $P < 0.05$, ** $P < 0.01$ compared to the baseline.

| Table 1 | Changes of investigated parameters in comparison of mean value to baseline in percent and numbers |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Baseline        | 5 ppm NO        | 10 ppm NO       | 30 ppm NO       | Iloprost        |
| MAP (mmHg)     | 96.6            | +0.7            | −0.1            | −0.4            | +3.8            |
| (%)            |                 | +0.7            | −0.1            | −0.4            | +3.8            |
| MPAP (mmHg)    | 32.4            | −3.7            | −5.3*           | −4.7*           | −7.6**          |
| (%)            |                 | −11.4           | −16.3*          | −14.5*          | −23.4**         |
| PCWP (mmHg)    | 18.3            | −2.9            | −3.8            | −3.2            | −5.9*           |
| (%)            |                 | −15.8           | −20.7           | −17.4           | −32.2*          |
| TPG (mmHg)     | 15.5            | −0.7            | −1.6            | −2.2            | −2.1            |
| (%)            |                 | −4.7            | −10.6           | −14.7           | −14             |
| PVR (dyne cm$^{-5}$) | 266            | −35.6           | −50.1*          | −39.8*          | −94.6**         |
| (%)            |                 | −13.3           | −18.8*          | −14.9*          | −35.4**         |
| SVR (dyne cm$^{-5}$) | 1526           | −50.8           | −88.3           | −10             | −180.6          |
| (%)            |                 | −3.3            | −5.8            | −0.7            | −11.8           |
| CI (l min m$^{-2}$) | 2.5              | ±0              | +0.1            | ±0              | +0.4*           |
| (%)            |                 | ±0              | +4              | ±0              | +16*            |
| SI (ml m$^{-2}$) | 31.1            | +1.2            | +2.9            | +0.9            | +4.3*           |
| (%)            |                 | +3.9            | +9.3            | +2.9            | +13.8*          |

* $P < 0.05$, ** $P < 0.01$. 

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reduced by 10 and 30 ppm NO and iloprost; the mean PVR values with iloprost (172 ± 60 dyn s cm⁻²) were lower than with NO (216 ± 98 dyn s cm⁻²) but differences were not significant. In addition to the effects on the pulmonary vascular bed we found a significant improvement of left heart function in patients treated with iloprost: while CI and SI remained unchanged during NO-inhalation we could document a significant increase of both CI (2.8 ± 0.7 versus 2.4 ± 0.6 l min⁻¹, P = 0.019) and SI (35.4 ± 8.8 versus 31 ± 7.1 ml m⁻², P = 0.022) after iloprost-inhalation. The pulmonary capillary wedge pressure was significantly reduced by iloprost. Due to the fact, that we found a simultaneous reduction in MPAP and PCWP, significant changes of transpulmonary gradient could not be documented.

Table I presents the changes in investigated parameters in number and percent in comparison to baseline. The alterations of oxygenation during inhalation of NO and iloprost are presented in Table 2. Significant improvement of SaO₂, SvO₂, and arterial oxygen tension (PaO₂) could be observed during inhalation of iloprost and all NO-concentrations, mixed venous oxygen tension (PvO₂)-values remained unchanged.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>5 ppm NO</th>
<th>10 ppm NO</th>
<th>30 ppm NO</th>
<th>Iloprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>SaO₂ (%)</td>
<td>96.6 ± 1.6</td>
<td>98.2 ± 1**</td>
<td>98.2 ± 1*</td>
<td>98.3 ± 0.9*</td>
<td>97.8 ± 1.4*</td>
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<tr>
<td>SvO₂ (%)</td>
<td>64.9 ± 5.4</td>
<td>67.7 ± 5</td>
<td>69.3 ± 4.1**</td>
<td>69.1 ± 4.5*</td>
<td>68.6 ± 6*</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>12.9 ± 4.9</td>
<td>19.9 ± 4.3**</td>
<td>20.1 ± 4.4**</td>
<td>18.9 ± 4.6**</td>
<td>18.5 ± 4.7**</td>
</tr>
<tr>
<td>PvO₂ (kPa)</td>
<td>4.2 ± 0.4</td>
<td>4.5 ± 0.5</td>
<td>4.4 ± 0.5</td>
<td>4.3 ± 0.8</td>
<td>4.5 ± 0.5</td>
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* Data are expressed as mean ± SD.
**P < 0.05.
***P < 0.01 compared to the baseline.

### 4. Discussion

In our study, we compared the effects of inhaled NO and aerosolized iloprost in patients with pulmonary hypertension due to chronic cardiac failure. Iloprost caused a significantly greater reduction in pulmonary arterial pressure and a tendentially greater decline of pulmonary vascular resistance than NO. The systemic vascular resistance and arterial blood pressure were not affected by both substances, furthermore we found no differences concerning the improvement of arterial and mixed venous oxygenation. In addition to the beneficial effects on the pulmonary vascular bed, iloprost caused a significant increase of CI and SI when compared with NO.

The use of NO and/or aerosolized PGI₂ for evaluation of heart transplant candidates with pulmonary hypertension has been described previously [8,18,19], the use of iloprost in those patients has not been presented before. All studies could show a selective pulmonary vasodilation with reduced pulmonary arterial pressure and an improved oxygenation. Inhaled NO in concentrations from 5 to 80 ppm have been shown to reduce an increased PVR in patients after heart transplantation [20], cardiac surgical patients [21], Acute Respiratory Distress Syndrome (ARDS) [22], and chronic pulmonary hypertension [23]. Haraldsson and coworkers described a selective dose-dependent decrease in PVR and transpulmonary gradient (TPG) at an inhaled concentration of 10 µg PGI₂ with no effects on systemic circulation [24]. The effects of PGI₂ and inhaled nitric oxide in view of the induction of pulmonary vasodilation of heart transplant candidates were comparable. Advantages of the prostacyclin-therapy were its lack of toxic reactions and an more easy administration [8].

Hoeper and coworkers described more potent effects of iloprost on the pulmonary vascular bed in patients with primary pulmonary hypertension when compared to inhaled NO [14]. We found comparable effects of iloprost in our patients with secondary pulmonary hypertension: The reduction of pulmonary arterial pressure was accompanied by an increase of CI output and SI when compared to NO. The improvement of left-heart function may be induced by a degree of systemic vasodilation in response to iloprost, but we found no reduction of mean arterial blood pressure or systemic vascular resistance compared to the baseline or to NO. Another possible explanation may be a direct positive inotropic effect of iloprost due to the prostanoiad- mediated increase of intracellular cAMP in cardiomyocytes [25]. In an experimental pig-model Kirsch-Wedel et al. could show that intravenously administered iloprost (8 µg kg⁻¹ min⁻¹) and PGI₂ (4 µg kg⁻¹ min⁻¹) caused a significant increase of left-ventricular myocardial contractility [26]. In contrast to other studies we found no increase of pulmonary capillary wedge pressure during NO inhalation [10], but a significant decrease of PCWP after iloprost inhalation.

In contrast to other authors, who found an increase of PCWP during pulmonary vasodilation, we could document a tendentially fall in PCWP with NO and a significant reduction of PCWP during iloprost-inhalation. Due to this fact, the resulting reduction of TPG was not significant. Taking into account the indications and contraindications of heart transplantation it seems necessary to consult more parameters than the TPG alone to reach a decision.

The hemodynamic effects of inhaled aerosolized iloprost
are in agreement with the documented effects of intravenous PGI₂ [13]. However, intravenous prostacyclin-administration is often limited by its effects on arterial blood pressure in patients with chronic heart failure [27]. This systemic hypotension limits the use of intravenous non-selective vasodilators in the evaluation of heart failure patients, especially in those with ischemic heart disease, and also in the postoperative treatment of patients after heart transplantation. In contrast, none of our patients developed worsening of arterial blood pressure or systemic vascular resistance or cardiac function.

In our study, the main disadvantage of NO inhalation was an increase in pulmonary artery pressure and pulmonary vascular resistance in four patients (28.6%). This observation is nearly identical with reports from Sibon et al. [28] and Hoeper et al. [14] who reported an increase of pulmonary artery pressure in 29 and 23%, and an increase of pulmonary vascular resistance in 17 and 31%, respectively, while using comparable concentrations of NO in patients with primary pulmonary hypertension. The possible mechanisms for this adverse reaction remains unclear, but we could demonstrate it again in patients with pulmonary hypertension due to chronic cardiac failure. Voelkel and coworkers have shown, that NO may become a potent pulmonary vasoconstrictor in the presence of hemosylate [29], the underlying mechanisms are still unknown. By contrast to NO, none of our patients treated with iloprost developed an increase of MPAP and/or PVR.

Langer and coworkers reported a case of right heart failure in the early postoperative course following orthotopic heart transplantation, successfully treated with inhalation of iloprost (16 μg, applied six times a day). The iloprost-inhalation resulted in a decrease of pulmonary vascular resistance (~23.5%), an increase of CI (24%), while no profound effect on systemic vascular resistance was observed (~2.8%) [15]. These findings are in agreement with our results and justify the use of iloprost in management of pulmonary hypertension and right heart insufficiency following heart transplantation. Nevertheless, the use of iloprost has to be evaluated in controlled trials. In another case report, Wittwer used an intensified pretreatment with intravenous prostacyclin and dobutamine, combined with an inhalative therapy with aerosolized iloprost, as a bridge to heart transplantation [16].

The results of our study show that inhaled aerosolized iloprost induces a reliable hemodynamic response in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. Compared to the effects of inhaled NO, iloprost was more effective in reducing pulmonary artery pressure and also induced an increase in CI and SI. Further advantages of iloprost inhalation are the lack of adverse reactions and toxic side effects and an easier administration. Due to this facts we recommend iloprost as a routine screening drug for vascular reactivity and we recommend further comparative studies to evaluate the place of iloprost in the management of perioperative pulmonary hypertension in cardiac transplantation in the near future.

References


