Modulation of Circulating Endothelin-1 and Big Endothelin by Nitric Oxide Inhalation Following Left Ventricular Assist Device Implantation

Frank D. Wagner, MD, PhD; Semih Buz, MD; Christoph Knosalla, MD, PhD; Roland Hetzer, MD, PhD; Berthold Hocher, MD, PhD

**Background**—Inhaled nitric oxide (iNO) is an established therapy in the treatment of pulmonary hypertension and right ventricular dysfunction following left ventricular assist device implantation. Since it is known that endothelin-1 contributes to pulmonary hypertension, and nitric oxide modulates endothelin-1 synthesis in vitro, we investigated the effects of iNO on circulating endothelin-1 and big endothelin following left ventricular assist device implantation.

**Methods and Results**—On weaning from cardiopulmonary bypass, 15 consecutive patients with secondary pulmonary hypertension after implantation of a left ventricular assist device were treated with iNO. Endothelin-1 and big endothelin plasma levels were measured preoperatively, on cardiopulmonary bypass prior to iNO, 12, 24, and 48 hour postoperatively, and 72 hour after cessation of iNO. Endothelin-1 levels were increased preoperatively (1.05±0.20 fmol/L), and were highest on cardiopulmonary bypass (1.65±0.27 fmol/L). During iNO therapy endothelin-1 and big endothelin decreased significantly (endothelin-1: 12 hour 1.24±0.18, 24 hour 0.93±0.20, and 48 hour 0.81±0.14 fmol/L); they were lowest 72 hour post-iNO (endothelin-1: 0.56±0.09 fmol/L). Plasma endothelin-1 concentrations and iNO dose were inversely correlated ($r = -0.657$, $P<0.015$). A significant correlation was also found between endothelin-1 versus PA pressures and PVR/SVR ratio, but not with CI and SVR.

**Conclusions**—Since it is known that endothelin-1 mediates pulmonary hypertension, we suggest a 2-fold effect of iNO therapy: firstly, a selective vasodilation of the pulmonary vasculature; and secondly, iNO mediated modulation of endothelin-1. (*Circulation*. 2003;108[supp II]:II-278-II-284.)

**Key Words:** nitric oxide ■ endothelin ■ heart-assist device

Pulmonary vascular resistance increases in patients with chronic left ventricular failure, which is thought to be due to dysregulation of the pulmonary vascular endothelium, and may ultimately lead to a structural remodeling in the pulmonary circulation. In patients with chronic left ventricular failure this may cause secondary pulmonary hypertension directly compromising right ventricular function.

Secondary pulmonary hypertension in end-stage heart failure is frequently associated with perioperative right ventricular failure after left ventricular assist device (LVAD) implantation. Vascular tone is thought to be controlled by a balanced endothelial release of vasodilators [eg, nitric oxide (NO), prostacyclin] and vasoconstrictors [eg, endothelin-1 (ET-1), angiotensin II]. Dysregulation of pulmonary vessels in chronic heart failure may be attributed to enhanced vasoconstriction mediated by ET-1. ET-1 plasma levels were found to be increased in primary and secondary pulmonary hypertension. The elevation of plasma ET-1 levels in chronic heart failure has been suggested to be due both to reduced pulmonary clearance and to increased production of ET-1 in the lungs. Pulmonary ET-1 spill-over correlated with pulmonary vascular resistance (PVR) in heart failure patients. As demonstrated by ET-1 immunoreactivity in pulmonary tissue, pulmonary hypertension is associated with an increased expression of ET-1 in pulmonary vascular endothelial cells. A recent study showing that blocking both endothelin receptors is an effective therapeutic strategy to treat pulmonary hypertension supports these findings. Endothelial dysfunction with ET-1 elevation and aggravation of pulmonary hypertension has also been demonstrated after cardiopulmonary bypass (CPB).

Administration of iNO selectively reduces pulmonary vascular resistance following LVAD implantation, suggesting that endothelial pulmonary synthesis of NO is initially compromised and that this physiological mediator is temporarily replaced by iNO. As a mechanism it is postulated that NO also inhibits endothelial production of endothelins. Univariate support with a LVAD may prove to be an ideal model to study effects on the pulmonary circulation, as the device fully unloads the left ventricle, and thus, native left ventricular function does not have to be accounted for.

So far, the expression of endothelins and the effects of iNO therapy on endothelins has not been studied in secondary pulmonary hypertension once heart failure is adequately

From the Deutsches Herzzentrum Berlin, Germany Charité der Humboldt Universität Berlin, Berlin, Germany. Correspondence to Dr Frank Wagner Deutsches Herzzentrum Berlin Augustenburger Platz 1 13353 Berlin, Germany. Phone: 30-4593-2111; Fax 30-4593-1852; E-mail Wagner@dhzb.de. © 2003 American Heart Association, Inc. *Circulation* is available at http://www.circulationaha.org DOI: 10.1161/01.cir.0000090630.48893.70
treated after LVAD implantation. Therefore, we investigated the effects of iNO on circulating ET-1 and big endothelin (big ET) following LVAD implantation.

Methods

Patients
Fifteen patients (1 female, 14 male) with a mean age of 48 years (range 37 to 60 years) were included in the study. Eight patients were diagnosed as having idiopathic and 7 patients ischemic cardiomyopathy. All patients were approved transplant candidates with end-stage heart failure presenting with a low cardiac output-syndrome unresponsive to maximal pharmacologic therapy and/or mechanical circulatory support with an IABP. In all patients, LVAD implantation was undertaken as an emergency procedure. Patients were included prior to surgery. All patients presented with right ventricular dysfunction at weaning from CPB due to secondary pulmonary hypertension, which was treated with iNO. To assist weaning from CPB epinephrine, dopamine, and dobutamine were used for inotropic support. In addition, 7 patients received a PDE-III inhibitor.

The investigation was approved by the institutional ethics committee and informed consent was obtained either from the patient or from the patient’s closest relatives.

LVAD Systems
Three different LVAD systems were used. The pneumatic driven pulsatile Berlin Heart LVAD, the electromagnetic driven pulsatile Novacor LVAS and the continuous flow MicroMed DeBakey VAD were implanted in 5 patients each.

NO Delivery
A Siemens Servo 300/NO-B respirator (Siemens-Elema, Sweden) with an integrated option for NO respiration was used in all patients throughout the study.

Study Design
All patients were treated with iNO intraoperatively to assist weaning from CPB. Weaning from iNO was initiated after hemodynamic stabilization and reduction of inotropic therapy by stepwise tapering of iNO dose at 1 to 5 ppm/hr from higher doses (>20 ppm NO) and at slower steps of maximally 1 ppm/hr at lower doses (<20 ppm NO), to prevent a possible rebound phenomenon.

PDE-III inhibitors, calcium antagonists and all nitrates were discontinued after surgery.

Measurements

Hemodynamic Parameters
Routine clinical monitoring included a central venous catheter, a femoral or radial artery catheter and a thermodilution-cuffed pulmonary-artery catheter (Baxter Healthcare, Irvine, CA). Arterial, central venous and pulmonary artery pressures were continuously measured with disposable transducers (Baxter Healthcare) and pulmonary occlusion pressures recorded at appropriate time points.

TABLE 1. Time Course of ET-1, Big ET and iNO Dose

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>CPB</th>
<th>12 h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h post iNO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1 (PA)</td>
<td>1.05±0.74</td>
<td>1.65±1.04</td>
<td>1.24±0.69</td>
<td>0.93±0.76</td>
<td>0.81±0.52</td>
<td>0.56±0.36</td>
</tr>
<tr>
<td>ET-1 (CV)</td>
<td>1.22±0.66</td>
<td>1.40±0.71</td>
<td>1.17±0.64</td>
<td>0.94±0.76</td>
<td>0.72±0.52</td>
<td>0.48±0.36</td>
</tr>
<tr>
<td>ET-1 (A)</td>
<td>1.49±1.15</td>
<td>1.48±0.79</td>
<td>1.23±0.82</td>
<td>1.00±0.89</td>
<td>0.70±0.59</td>
<td>0.57±0.37</td>
</tr>
<tr>
<td>Big ET-1 (PA)</td>
<td>3.46±2.04</td>
<td>3.67±2.16</td>
<td>5.04±4.92</td>
<td>3.76±1.89</td>
<td>4.31±3.86</td>
<td>2.29±0.97</td>
</tr>
<tr>
<td>Big ET-1 (CV)</td>
<td>3.64±2.74</td>
<td>5.95±4.37</td>
<td>3.64±1.88</td>
<td>4.12±3.27</td>
<td>2.18±0.90</td>
<td>0.0004</td>
</tr>
<tr>
<td>Big ET-1 (A)</td>
<td>3.27±1.96</td>
<td>3.29±2.24</td>
<td>5.51±4.95</td>
<td>3.47±2.17</td>
<td>3.93±2.56</td>
<td>2.12±0.82</td>
</tr>
<tr>
<td>iNO (ppm)</td>
<td>—</td>
<td>—</td>
<td>27±16</td>
<td>16±19</td>
<td>6±10</td>
<td>—</td>
</tr>
</tbody>
</table>

ET-1 = endothelin-1; Big ET = big endothelin; iNO = inhaled nitric oxide; CPB = cardiopulmonary bypass; 72 h NO post iNO = 72 h after cessation of inhaled nitric oxide; PA = pulmonary artery sample; CV = central-venous sample; A = arterial sample. Mean±SD.
were measured to be lowest 72 hours after cessation of iNO therapy (Table 1). The highest big ET levels were measured 12 hours postoperatively and the lowest concentrations of big ET 72 hours after cessation of iNO therapy. Therapy with iNO had been steadily reduced postoperatively from a mean dose of 27±16 at 12 hours to 6±10 ppm at 48 hours (Table 1).

### Time Course of Hemodynamic Parameters
The details of hemodynamic effects with time of iNO treatment are shown in Table 2.

Preoperative CI was 2.6±0.6 L/min/m², 12 hours postoperatively 3.1±0.7 L/(min/m²) and 3.2±0.6 L/(min/m²) 72 hours after weaning from iNO (P<0.0001) (Table 2).

PA pressures and PCWP were increased preoperatively due to congestive heart failure with secondary pulmonary hypertension. Postoperatively these pressures fell significantly and over time were significantly lower than pretreatment values. PAM at 12 hours postoperatively (24±7 mm Hg) was significantly lower than preoperatively (38±10 mm Hg) and remained significantly lower than preoperatively up to 72 hours after cessation of iNO therapy (P<0.0001) (Table 2).

PVR was measured preoperatively to be 255±109 dynes×cm⁻⁵ and postoperatively it fell significantly: at 12 hours to 217±61 dynes×cm⁻⁵ and 204±64 dynes×cm⁻⁵ 72 hours after cessation of iNO therapy (P<0.03) (Table 2). The MAP, SVR, and CVP were not significantly altered during the postoperative course. Epinephrine dose was significantly higher postoperatively [0.11±0.02 µg/(kg/min)] and was progressively reduced to 0.02±0.01 µg/kg/min (P<0.0001) 72 hours after cessation of iNO therapy (Table 2).

### Correlations

#### Baseline Values
Preoperatively central-venous, pulmonary arterial, and artery plasma levels of ET-1 and big ET significantly correlated with PA pressures, PVR and PCWP. No correlation could be established for ET-1 or big ET plasma levels versus CI, arterial pressures, SVR and CVP. Correlations between central-venous plasma levels for ET-1 and big ET and preoperative hemodynamic parameters are given in Table 3. The results of linear regression analysis for pulmonary artery and arterial ET-1 and big ET plasma levels are similar, but are not shown in detail.

#### Correlations between ET-1 and Big ET With NO Dose
To analyze the impact of iNO therapy on ET-1 and big ET plasma levels with time of treatment, the absolute changes of the mean iNO dose between 12 hours and 48 hours postoperatively were correlated with the absolute differences of ET-1 and big ET plasma concentrations during the same time interval.

A significant inverse correlation for ET-1 plasma levels versus the mean iNO dose was found in central-venous and pulmonary artery plasma samples (Table 4 and Figure 2). A significant inverse correlation was also found for arterial big ET plasma levels (Table 4).

There was no statistically significant correlation between the mean administered iNO dose and the arterial ET-1 plasma levels.

### TABLE 2. Time Course of Hemodynamic Parameters and Epinephrine Dose

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>12 h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h post iNO</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>2.6±0.6</td>
<td>3.1±0.7</td>
<td>3.1±0.6</td>
<td>3.3±0.8</td>
<td>3.2±0.6</td>
<td>0.08</td>
</tr>
<tr>
<td>PAM</td>
<td>38±10</td>
<td>24±7</td>
<td>25±7</td>
<td>27±6</td>
<td>25±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PA syst</td>
<td>48±12</td>
<td>31±9</td>
<td>32±9</td>
<td>35±9</td>
<td>37±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PA diast</td>
<td>29±8</td>
<td>18±6</td>
<td>19±6</td>
<td>20±5</td>
<td>18±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCWP</td>
<td>22±8</td>
<td>7±5</td>
<td>9±5</td>
<td>10±5</td>
<td>8±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR</td>
<td>255±109</td>
<td>217±61</td>
<td>195±60</td>
<td>210±66</td>
<td>204±64</td>
<td>0.03</td>
</tr>
<tr>
<td>CVP</td>
<td>11±5</td>
<td>10±3</td>
<td>10±3</td>
<td>10±2</td>
<td>9±3</td>
<td>n.s.</td>
</tr>
<tr>
<td>MAP</td>
<td>73±14</td>
<td>74±7</td>
<td>73±10</td>
<td>78±13</td>
<td>77±8</td>
<td>n.s.</td>
</tr>
<tr>
<td>SVR</td>
<td>974±309</td>
<td>889±197</td>
<td>879±253</td>
<td>836±260</td>
<td>891±171</td>
<td>n.s.</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.07±0.02</td>
<td>0.11±0.02</td>
<td>0.07±0.01</td>
<td>0.05±0.09</td>
<td>0.02±0.01</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

72 h post iNO=72 h after cessation of inhaled nitric oxide; CI=cardiac index (L/min/m²); PAM=mean pulmonary artery pressure (mm Hg); PA syst=systolic pulmonary artery pressure (mm Hg); PA diast=diastolic pulmonary artery pressure (mm Hg); PCWP=pulmonary capillary wedge pressure (mm Hg); PVR=pulmonary vascular resistance (dynes×cm⁻²); CVP=central-venous pressure (mm Hg); MAP=mean arterial pressure (mm Hg); SVR=systemic vascular resistance (dynes×cm⁻²); Mean±SD.
levels on the one hand and between the mean administered iNO dose and the central-venous and pulmonary artery big ET levels on the other hand (Table 4).

Correlations between ET-1 and Big ET With Hemodynamic Parameters
The percent changes of ET-1 and big ET plasma concentrations from central-venous blood samples between 12 hours and 48 hours postoperatively were correlated with the percent differences of the hemodynamic parameters during the same time interval.

The percent changes of ET-1 plasma levels versus the percent differences of CI, PCWP, SVR, and the administered epinephrine dose (Table 5).

TABLE 4. Correlations ET-1 and Big ET vs. Mean iNO Dose

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1 vs. iNO</td>
<td>−0.657</td>
<td>(&lt;0.015)</td>
</tr>
<tr>
<td>ET-1 (PA) vs. iNO</td>
<td>−0.587</td>
<td>(&lt;0.045)</td>
</tr>
<tr>
<td>ET-1 (A) vs. iNO</td>
<td>−0.567</td>
<td>(n.s.)</td>
</tr>
<tr>
<td>Big ET-1 (PA) vs. iNO</td>
<td>−0.445</td>
<td>(n.s.)</td>
</tr>
<tr>
<td>Big ET-1 (A) vs. iNO</td>
<td>−0.503</td>
<td>(n.s.)</td>
</tr>
<tr>
<td>Big ET-1 (A) vs. iNO</td>
<td>−0.636</td>
<td>(&lt;0.048)</td>
</tr>
</tbody>
</table>

The percent changes of ET-1 significantly correlated versus the percent differences of the PVR/SVR ratio indicating pulmonary vascular selectivity of a vasodilating compound, but not versus the percent changes of the PVR (Table 5).

No correlation was found for the percent changes of ET-1 plasma levels versus the percent differences of CI, PCWP, SVR, and the administered epinephrine dose (Table 5).

Big ET plasma levels did not correlate with hemodynamic parameters.

Discussion
The endothelium plays a key role in the regulation of vascular tone, resulting from a balanced, endogenous release of vasoconstrictors in relation to vasodilators. In chronic heart failure pulmonary vascular resistance increases and is thought to be due, among other mechanisms, to dysregulation of the pulmonary vascular endothelium with an impaired release of NO and increased expression of ET-1. A basal production of NO, thought to be necessary to keep up the lower pulmonary vascular tone, appears to be deficient in patients with severe heart failure and may contribute to the development of secondary pulmonary hypertension.

Severe heart failure is associated with increased ET-1 plasma levels correlating with the degree of heart failure and the extent of pulmonary hypertension. The lungs are an important organ both for the production and elimination of ET-1, a pulmonary spill-over of ET-1 correlating well with the PVR measured in chronic heart failure. It has been shown that NO inhibits the in vitro synthesis of ET-1. By activation of the ETB receptor, ET-1 is able to stimulate NO synthesis. The potent endogenous vasodilator NO and the potent endogenous vasoconstrictor ET-1 thus are an important feedback loop with a negative feedback mechanism.

It was demonstrated in in vitro studies and studies in healthy subjects that NO may inhibit the synthesis of ET-1. The effects of exogenously administered iNO on circulating plasma levels of ET-1 and big ET and the associated hemodynamic changes in the clinical use of iNO have not...
TABLE 5. Correlations of ET-1 vs. Postoperative Hemodynamic Parameters

<table>
<thead>
<tr>
<th></th>
<th>PA syst</th>
<th>PA diast</th>
<th>PAM</th>
<th>PVR/SVR</th>
<th>PVR</th>
<th>PCWP</th>
<th>CI</th>
<th>MAD</th>
<th>CVP</th>
<th>SVR</th>
<th>Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET-1</td>
<td>0.561</td>
<td>0.569</td>
<td>0.593</td>
<td>0.577</td>
<td>0.385</td>
<td>0.068</td>
<td>0.410</td>
<td>0.415</td>
<td>0.440</td>
<td>0.253</td>
<td>0.105</td>
</tr>
</tbody>
</table>

The correlations between the percent differences of ET-1 plasma levels vs. the percent hemodynamic differences 12 hours vs. 48 hours postoperatively are given. ET-1 = Endothelin-1; big ET = big endothelin; PA syst = systolic pulmonary artery pressure (mm Hg); PA diast = diastolic pulmonary artery pressure (mm Hg); PAM = mean pulmonary artery pressure (mm Hg); PVR/SVR = pulmonary vascular resistance (dynes-cm⁻²); PCWP = pulmonary capillary wedge pressure (mm Hg); CI = cardiac index (L/min/m²); MAP = mean arterial pressure (mm Hg); CVP = central-venuous pressure (mm Hg); SVR = systemic vascular resistance (dynes-cm⁻²). Epinephrine (µg/kg/min). Correlation coefficients and p-values are given.

been previously described. In the setting of LVAD implantation iNO may not only substitute for a physiologically deficient NO release in the pulmonary circulation, but may also modulate ET-1 and big ET production.

To our knowledge, our study investigated for the first time the effects of iNO on circulating ET-1 and big ET plasma levels in patients with secondary pulmonary hypertension after LVAD implantation.

As expected in patients with end-stage heart failure preoperative ET-1 and big ET plasma levels were elevated and correlated significantly versus PA pressures, PVR, and PCWP, but not versus CI, CVP, MAP, and SVR, which is in keeping with other reports.

An aggravation of pulmonary hypertension during and after CPB, among other reasons, has been explained by CPB induced endothelial dysfunction. A decrease of the basal endothelial NO release has been discussed as one possible explanation. Investigations on changes in basal NO production induced by the CPB generated conflicting evidence with divergent results. As the reduction in basal NO release did not correlate with the extent of CPB induced pulmonary hypertension, other reasons have been discussed, such as the release of ET-1. An increase in ET-1 plasma levels during CPB has been related to a PVR increase and correlated with the PVR/SVR ratio in patients with pulmonary hypertension.

In our patients with secondary pulmonary hypertension the highest ET-1 plasma levels were measured on CPB and it is suggested that ET-1 influenced the postoperatively increased PVR following CPB, which is in accordance with the studies published.

During iNO therapy plasma ET-1 significantly decreased up to 48 hours postoperatively, and ET-1 concentrations were lowest 72 hours after weaning from iNO. Plasma levels of big ET were highest 12 hours postoperatively and lowest 72 hours after cessation of iNO therapy.

Simultaneously with a decrease of ET-1 and big ET plasma levels during the postoperative course by unloading of the left ventricle through the LVAD and treatment of secondary pulmonary hypertension by iNO administration a significant hemodynamic improvement was seen. Postoperatively PA pressures, PCWP and PVR decreased significantly whereas CI increased, as the epinephrine dose could be drastically reduced; MAP, SVR, and CVP were not significantly altered.

During iNO therapy between 12 and 48 hours postoperatively a significant correlation between the percent changes of the central-venous ET-1 plasma levels and the percent differences of the PA pressures and the PVR/SVR ratio was seen, whereas CI, PCWP, MAP, SVR, and administered epinephrine dose did not correlate, which reflects pulmonary vascular selectivity of a vasodilator such as iNO. There was no correlation of big ET plasma levels versus hemodynamic parameters.

It is of note that during the course of iNO therapy between 12 and 48 hours postoperatively both an inverse correlation of the respective central-venous and pulmonary artery ET-1 plasma levels versus the mean NO dose and a correlation of plasma ET-1 levels versus the PA pressures and the PVR/SVR ratio were demonstrated. Thus a direct relationship between iNO therapy and ET-1 plasma levels on the one hand and the associated pulmonary hemodynamic changes on the other hand may be assumed. Weaning individual patients from iNO therapy in this study was based on improvement in CI. Thus, the decline of endothelins in parallel with a reduction in pulmonary pressures is most likely due to iNO therapy, and not related to the immediate effects of improved systemic hemodynamics. We suggest that a faster reduction of iNO dose implies a weaker NO-dependent inhibition of ET-1 release, as a quickly lowered iNO dose was associated with higher plasma ET-1 concentrations, and vice versa.

A significant correlation between the decrease of ET-1 and big ET plasma levels versus a decrease of PA pressures has also been demonstrated following administration of vasodilators in severe heart failure and the reduction of endothelins had been attributed to improved hemodynamics due to vasodilator therapy. Although these findings are in accordance with our results, contrary to the quoted study using systemic vasodilators, we administered the selective pulmonary vasodilator iNO instead. Using iNO the effects on pulmonary and systemic hemodynamics and on endothelins may be different to the effects of administering a systemic vasodilator. In addition, the effects of iNO administration under the special circumstances of complete unloading of the failing left ventricle and relief of pulmonary venous congestion by the LVAD are focused on the pulmonary circulation and the right heart.
Physiological endothelial NO release antagonizes the vasoconstricting effects of endothelin; but in pulmonary hypertension the ability of the endothelium to release NO is lost. Administration of iNO thus substitutes for a physiological mediator in the state of deficient endothelial dependent vasodilation. In addition it may be assumed that iNO therapy not only replaces a diminished pulmonary NO release by exogenous administration but may also modulate the release of endothelins in patients following LVAD implantation.

Limitations of the study are that a control group was not included, as in view of the established beneficial effects of iNO in this patient group it was thought not to be justified by the institutional ethics committee to withhold iNO therapy for study reasons. Despite the fact that the left ventricle is fully unloaded following LVAD placement pulmonary hypertension frequently persists, which may be attributed to pulmonary endothelial dysfunction. We have previously shown the efficacy of iNO in treating pulmonary hypertension and consecutive right ventricular dysfunction with a dramatic hemodynamic improvement due to selective pulmonary vasodilation in this patient group, and have since then introduced iNO in routine therapy. Although LVAD implantation is a potential confounder in this study, given the effects of iNO therapy a causal relationship to the hemodynamic course and endothelin levels is the most likely explanation. Undoubtedly the release of endothelins was modulated following LVAD implantation. The question is, whether the decrease of ET-1 and big ET plasma levels was a direct inhibitory effect of iNO or due to progressive hemodynamic improvement. That NO can inhibit ET-1 synthesis has previously been demonstrated in vitro and in healthy volunteers. Recently, it was demonstrated that NO inhibits ET-1 production by suppression of nuclear factor B and NO gas was shown to decrease ET-1 mRNA in cultured pulmonary artery endothelial cells. In infants with persistent pulmonary hypertension the newborn ET-1 levels decreased with iNO therapy and the changes in ET-1 levels with iNO were inversely correlated with changes in arterial PO2. These findings are in line with the interpretation, that in our study iNO suppressed the release of endothelins, resulting in reduction of pulmonary hypertension, although in view of the potential hemodynamic effects of LVAD implantation this question cannot be conclusively answered. Inhibition of endothelins in pulmonary hypertension and heart failure by administering endothelin antagonists is increasingly being recognized as a therapeutic principle. Regardless of the underlying mechanisms, the decrease of endothelins in parallel with improved hemodynamics provides insight in pulmonary vascular changes in LVAD recipients.

In conclusion, iNO may not only induce pulmonary selective vasodilation by replacing a deficient endogenous NO production in secondary pulmonary hypertension, but it may also modulate ET-1 and big ET. Pulmonary selective vasodilation with iNO is only needed as an intermittent therapy. With left ventricular failure being effectively treated by mechanical unloading through the LVAD, again a physiological balance may develop between the antagonists NO and endothelins in the pulmonary circulation, thus resolving dysfunction of the pulmonary vascular endothelium.

Acknowledgments
This study was partially supported by grant DFG Ho1665/5-1.

References
Modulation of Circulating Endothelin-1 and Big Endothelin by Nitric Oxide Inhalation Following Left Ventricular Assist Device Implantation
Frank D. Wagner, Semih Buz, Christoph Knosalla, Roland Hetzer and Berthold Hocher

Circulation. 2003;108:II-278-II-284
doi: 10.1161/01.cir.000090630.48893.70

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/108/10_suppl_1/II-278