A Comparison of the Acute Hemodynamic Effects of Inhaled Nitric Oxide and Aerosolized Iloprost in Primary Pulmonary Hypertension

Marius M. Hoeper, MD,* Horst Olschewski, MD,† Hossein A. Ghofrani, MD,† Heinrike Wilkens, MD,‡ Joerg Winkler, MD,§ Mathias M. Borst, MD,¶ Jost Niedermeyer, MD,* Helmut Fabel, MD,* Werner Seeger, MD,† and the German PPH Study Group¶

Hannover, Germany

OBJECTIVE
We sought to compare the acute hemodynamic effects of inhaled nitric oxide (NO) and aerosolized iloprost in primary pulmonary hypertension (PPH).

BACKGROUND
Inhalation of the stable prostacyclin analogue iloprost has recently been described as a novel therapeutic strategy for PPH and may offer an alternative to continuous intravenous infusion of prostacyclin or inhalation of NO.

METHODS
During right heart catheterization, 35 patients with PPH sequentially inhaled 40 ppm of NO and 14 to 17 µg of iloprost, and the effects on hemodynamics and blood gases were monitored.

RESULTS
Both NO and iloprost caused significant increases in cardiac output, mixed-venous oxygen saturation and stroke volume as well as significant decreases in pulmonary artery pressure and pulmonary vascular resistance, whereas only inhaled iloprost significantly increased the arterial PO2 (p < 0.01). Compared with inhaled NO, aerosolized iloprost was more effective in reducing pulmonary artery pressure (2.8 ± 0.3 vs. 2.4 ± 0.8 mm Hg; p < 0.001) and the pulmonary vascular resistance (247 ± 340 dyne·s·cm⁻² vs. 183 ± 305 dyne·s·cm⁻²; p < 0.0001). Furthermore, aerosolized iloprost caused a significantly greater increase of the cardiac output compared with NO (+0.7 ± 0.6 liter/min vs. +0.3 ± 0.4 liter/min; p = 0.0002) and had a more pronounced effect on the mixed-venous oxygen saturation (p = 0.003).

CONCLUSIONS
During acute drug testing, aerosolized iloprost was more potent than inhaled NO as a pulmonary vasodilator in PPH at the doses used in this study. (J Am Coll Cardiol 2000;35:176–82) © 1999 by the American College of Cardiology

The most significant improvement in the treatment of severe primary pulmonary hypertension (PPH) in recent years has been the introduction of continuous intravenous prostacyclin (PGI₂) infusion, which has been shown to improve exercise tolerance and survival (1–7). This form of treatment, however, has major drawbacks. Intravenous PGI₂ can cause substantial side effects such as systemic hypotension, nausea, vomiting and diarrhea, headache and a worsening of gas exchange (4,5,8). Moreover, the long-term therapeutic application of PGI₂ requires a permanent central venous catheter, which may result in thrombotic or infectious complications. Furthermore, the continuous intravenous administration of PGI₂ leads to tachyphylaxis and therefore requires permanent dose escalation, and there is a substantial risk of severe rebound phenomena when the infusion is interrupted (5).

An alternative drug recently proposed for the treatment of pulmonary hypertension is nitric oxide (NO) (9–11). Acute vasoreactivity testing with inhaled NO has been introduced as a safe means to identify patients who can be expected to benefit from long-term treatment with oral vasodilators (10,12). In addition, the identification of patients who exhibit a marked reactivity of the pulmonary vascular bed is a valuable prognostic marker (13). For theoretical reasons, inhaled NO offers several advantages over intravenous PGI₂ for long-term treatment of PPH. Nitric oxide is a potent and selective pulmonary vasodilator with virtually no systemic side effects, due to rapid inactivation by hemoglobin binding after entering the vascular space. In addition, unlike systemic vasodilators, inhaled NO...
acts selectively in ventilated areas of the lung, thus causing redistribution of blood flow from shunt areas to ventilated areas (14). These factors may be especially relevant for treatment of advanced right heart failure in which any systemic vasodilator carries the risk of worsening hypoxia and hypotension. However, because of its short half-life, NO has to be administered continuously, and even brief interruptions of the supply may cause dangerous rebound pulmonary hypertension (15). In addition, to our knowledge, there are currently no controlled data suggesting a long-term benefit from inhaled NO for patients with PPH.

Recently, Olschewski et al. (16) described the use of aerosolized iloprost for severe pulmonary hypertension. Iloprost is a carbacyclin analogue of PGI2 that has a plasma half-life of 20 to 30 min (17,18). When inhaled, iloprost seems to cause preferential pulmonary vasodilation that lasts for about 1 to 2 h (16). This form of treatment appears to be promising because it may combine the beneficial long-term effects of continuous intravenous PGI2 with the advantages of inhaled NO without the problems of continuous intravenous administration.

Unlike NO, inhaled iloprost may also act in the systemic circulation, as the molecule will not be rapidly inactivated in the pulmonary vascular bed. It is currently not known to what extent systemic effects might add to the local pulmonary effects. To further evaluate the pharmacodynamic profile of aerosolized iloprost, we compared the acute hemodynamic effects of inhaled NO and aerosolized iloprost in patients with PPH.

METHODS

Patient population. This investigation was part of a German multicenter trial initiated to evaluate the efficacy of aerosolized iloprost in severe pulmonary hypertension. In this study, only patients were included who fulfilled the diagnostic criteria of the National Institutes of Health registry for PPH (19).

Patients were excluded from the study when they suffered from significant coagulopathy, when they had severe airway obstruction, when they suffered from a coronary or cerebrovascular event within three months before the study or when there was significant impairment of liver and kidney function. Any concomitant medication except for anticoagulation was kept unchanged. Treatment with oral anticoagulants was stopped until the international normalized ratio was lower than 1.5, and all patients received intravenous heparin (400 to 800 U/h) while the catheters were inserted.

The study protocol was reviewed and approved by the institutional ethical committees of all participating centers, and all patients provided written informed consent before entering the study.

Hemodynamic monitoring. For the purpose of this study, the patients were admitted to an intensive care unit. An 8F introducer sheath was placed into the right or left internal jugular vein and a triple lumen 7.5F flow-directed Swan-Ganz-catheter (Baxter, Edwards, California) was advanced into the pulmonary artery. Correct positioning of the catheter was verified by chest X-ray or fluoroscopy. A 5F Teflon catheter was inserted into a femoral artery. Transducers were positioned at the midaxillary line and zeroed at atmospheric pressure. Systolic, diastolic and mean pulmonary and systemic arterial pressures as well as the right atrial pressure were monitored continuously, and the pulmonary capillary wedge pressure (PCWP) was determined at baseline and at the end of each evaluation period. The cardiac output (CO) was measured in triplicate by the thermodilution technique (Cardiac Output Computer; Baxter, Edwards, California) with ice-cold isotonic sodium chloride solution, and the cardiac index was calculated by dividing the CO through the body surface area. The pulmonary vascular resistance was calculated as mean pulmonary artery pressure, – PCWP (PAPmean – PCWP) * 80/CO. The systemic vascular resistance was calculated as mean systemic blood pressure – right atrial pressure (SAP – RAP) * 80/CO. The heart rate and the transcutaneous arterial oxygen saturation were monitored continuously.

Blood samples. Arterial and mixed-venous blood samples were obtained simultaneously for determination of PO2, PCO2, pH, base excess and SO2 (ABL 520, Radiometer, Copenhagen).

Vasodilator protocol. After insertion of the catheters, the patients were allowed to rest for at least 15 min. The patients were breathing through an inhalation device (raindrop nebulizer) that had been developed for the application of iloprost (Ilomedin, Schering AG, Berlin, Germany). When the arterial oxygen saturation was <90%, supplemental oxygen was added to the inhalation device until the oxygen saturation was >90%, and the oxygen flow was kept constant throughout the study. After the baseline variables had been obtained (baseline 1), NO was added to the inspiratory limb of the device until an expiratory concentration of 40 ppm was reached. The NO concentration was measured using the electrochemical technique (MicroGas Nitric Oxide Monitor, Med In, Munich, Germany). After 15 min of inhaling NO at 40 ppm, a complete evaluation of hemodynamics and blood gases was performed. Thereafter, NO was discontinued. Thirty minutes later, another set of baseline hemodynamics was recorded (baseline 2), and the inhalation of iloprost (Iloneb, Nebutec, Elsenfeld, Germany) was started until the international normalized ratio was 1.5, and all patients received intravenous heparin (400 to 800 U/h) while the catheters were inserted.

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Germany) was started. Fifty micrograms of iloprost was diluted in 5 ml of isotone saline solution and nebulized in the device described above for 15 min, which resulted in an aerosolized dose between 14 and 17 μg. This approach has been shown to provide a safe and effective means for delivery of iloprost aerosol (16). Complete sets of hemodynamic measurements and blood gases were performed before inhalation, in the last minute of the inhalation period and every 15 min thereafter for up to 1 h.

**Statistical analysis.** The results are expressed as mean ± SD (range) unless indicated otherwise. The individual preinhalation and postinhalation variables were compared by means of the Wilcoxon signed-rank test. This test was also applied to compare the pre-post differences of NO inhalation and iloprost inhalation (both measured immediately before and at the end of the inhalation period). The calculated significance levels were used as the criterion to state differences between the inhalative agents (explorative strategy). The Friedman test was employed to test for global changes from baseline during repeated measurements over 1 h after inhalation. To further settle for significant differences at different time points (repeated measurements), the upper 95% confidence limits for medians were calculated, and a significant effect was assumed when the 95% confidence interval was below the baseline value. All tests were two-sided. Significance was set at p < 0.05.

**RESULTS**

**Study population.** We studied 35 patients, 19 women and 16 men with PPH. The mean age was 46 ± 13 years (range, 20 to 76 years). Six patients were New York Heart Association (NYHA) class II, 18 patients were NYHA class III and 11 patients were NYHA class IV. Fifteen patients were receiving low-dose calcium-channel blockers (maximum daily dose of 40 mg nifedipine or 5 mg felodipine). The baseline hemodynamic variables are shown in Table 1.

**Hemodynamic responses.** The hemodynamic parameters and the oxygenation status at baseline and at the end of inhalation with NO and iloprost are shown in Table 1 and in Fig. 1A to C. During inhalation of NO, the mean pulmonary arterial pressure declined by 4.3 ± 8.8 mm Hg (range, +11 to −27 mm Hg; p = 0.008 vs. baseline), whereas the systemic arterial pressure and the systemic vascular resistance remained unchanged. The CO increased by 0.3 ± 0.4 liter/min (range, −0.37 to +1.11 liter/min; p = 0.001 vs. baseline), and the stroke volume increased by 4.2 ± 8.2 ml (range, −15.4 to +26.4 ml; p = 0.009 vs. baseline). The right atrial pressure fell by 1.1 ± 2.1 mm Hg (range, −6 to +2 mm Hg; p = 0.004 vs. baseline). The mixed-venous oxygen saturation rose by 2.5% ± 6.7% (range, −12% to +19.9%; p = 0.06 vs. baseline). The pulmonary vascular resistance declined by 183 ± 305 dynes (range, −1,258 dynes to +318 dynes; p = 0.0006 vs. baseline). The arterial PaO2 was minimally affected during inhalation of NO (+1.8 ± 14.1 mm Hg; p = 0.84).

Aerosolized iloprost caused a decline of the mean pulmonary arterial pressure by −8.3 ± 7.5 mm Hg (range, −33 to ±0 mm Hg; p < 0.001 vs. baseline). There was a statistically significant difference between the effects of NO and iloprost on the mean pulmonary artery pressure (p = 0.0001). Furthermore, iloprost caused an increase of the CO by 0.7 ± 0.6 liter/min (range, −0.1 to +3.3 liter/min). This was also statistically significant when tested against baseline (p <

**Table 1.** Hemodynamic Variables and Blood Gases in Response to Inhaled NO and Aerosolized Iloprost

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1 (Before NO)</th>
<th>NO (40 ppm)</th>
<th>Baseline 2 (Before Iloprost)</th>
<th>Iloprost (14–17 μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>84 ± 17</td>
<td>83 ± 17</td>
<td>87 ± 16</td>
<td>86 ± 17</td>
</tr>
<tr>
<td>SAPmean (mm Hg)</td>
<td>93 ± 15</td>
<td>94 ± 15</td>
<td>89 ± 15</td>
<td>86 ± 13†</td>
</tr>
<tr>
<td>PAPmean (mm Hg)</td>
<td>59 ± 11</td>
<td>55 ± 15*</td>
<td>60 ± 11</td>
<td>52 ± 13†</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>8 ± 6</td>
<td>7 ± 6*</td>
<td>8 ± 6</td>
<td>7 ± 5*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>7 ± 3</td>
<td>6 ± 3</td>
<td>7 ± 3</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>CO (liter/min)</td>
<td>3.4 ± 1.1</td>
<td>3.7 ± 1.2*</td>
<td>3.5 ± 1.2</td>
<td>4.2 ± 1.2†</td>
</tr>
<tr>
<td>CI (liter/min/m²)</td>
<td>2.0 ± 0.7</td>
<td>2.1 ± 0.7*</td>
<td>2.0 ± 0.7</td>
<td>2.4 ± 0.7†</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>43 ± 18</td>
<td>47 ± 19*</td>
<td>42 ± 18</td>
<td>51 ± 16†</td>
</tr>
<tr>
<td>SVR (dynes/cm⁻⁵)</td>
<td>2,127 ± 670</td>
<td>2,024 ± 642</td>
<td>2,017 ± 741</td>
<td>1,597 ± 519†</td>
</tr>
<tr>
<td>PVR (dynes/cm⁻⁵)</td>
<td>1,342 ± 518</td>
<td>1,159 ± 587*</td>
<td>1,367 ± 492</td>
<td>920 ± 387†</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>66 ± 14</td>
<td>68 ± 15</td>
<td>66 ± 12</td>
<td>73 ± 18†</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>90 ± 12</td>
<td>92 ± 6</td>
<td>91 ± 5</td>
<td>94 ± 4†</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>58 ± 14</td>
<td>60 ± 13*</td>
<td>59 ± 15</td>
<td>66 ± 13†</td>
</tr>
</tbody>
</table>

CI = cardiac index; CO = cardiac output; HR = heart rate; NO = nitric oxide; PaO₂ = arterial oxygen tension; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SaO₂ = arterial oxygen saturation; SAP = systemic arterial blood pressure; SV = stroke volume; SvO₂ = mixed-venous oxygen saturation; SVR = systemic vascular resistance.

*p < 0.05 for NO vs. baseline 1 and iloprost versus baseline 2, respectively.

†p < 0.05 for iloprost vs. NO.
In addition, iloprost caused a significant increase of the stroke volume by 8.8 ± 9.6 ml (range, −12.2 to +38.2 ml; p < 0.0001 vs. baseline and p = 0.005 vs. NO). The right atrial pressure fell by 1.5 ± 2.5 mm Hg (range, −9 to +3 mm Hg; p = 0.002 vs. baseline), which was not significantly different from the change of the right atrial pressure during inhalation of NO. The mixed venous oxygen saturation rose by 7.5% ± 6.5% (range, +0.4% to 29.1%; p < 0.0001 vs. baseline and p = 0.003 vs. NO). The pulmonary vascular resistance declined by 447 ± 340 dynes (range, −42 dynes to −1,788 dynes). This difference was highly significant when compared with baseline (p < 0.0001) and when compared with NO (p < 0.0001).

The systemic vascular resistance was also significantly reduced by iloprost (−420 ± 384 dynes; range, +99 to −1,318 dynes; p < 0.0001 vs. baseline and p < 0.0001 vs. NO), and the systemic arterial pressure declined by −3.5 ± 7.0 mm Hg (range, −21 to +14 mm Hg; p < 0.01 vs. baseline; p = 0.002 vs. NO). Clinically relevant systemic hypotension (i.e., a drop in the systolic blood pressure below 90 mm Hg) occurred in none of our patients during inhalation of iloprost.

Furthermore, aerosolized iloprost resulted in an increase of the arterial PO2 by 6.9 ± 14.8 mm Hg (range, −15 to +62 mm Hg) that was statistically significant in comparison to baseline (p = 0.01) and in comparison to NO (p = 0.02). Heart rate and PCWP were not significantly affected by either NO or iloprost.

**Figure 1.** Comparison of the effects of inhaled nitric oxide (NO, 40 ppm for 15 min) and aerosolized iloprost (14 to 17 μg over 15 min) on pulmonary artery pressure (A), cardiac output (B) and pulmonary vascular resistance (C) in 35 patients with primary pulmonary hypertension. Dots represent the individual responses compared to baseline, expressed as percentage. A location below the line of identity indicates a more pronounced effect of iloprost, while a location above the line of identity reflects a more pronounced effect of NO.
There was a significant correlation between the effects of NO and iloprost on the pulmonary vascular resistance \((r = 0.63; p < 0.01)\) but only in four cases, the NO response was greater or equal to the iloprost response (Fig. 1C). In addition, inhaled NO led to a paradoxical increase of the pulmonary vascular resistance in six of our patients (17%) and of the pulmonary artery pressure in 10 of our patients (29%), which did not occur with iloprost. Of the 24 patients with a minor response to NO (defined as a pulmonary vascular resistance decrease of \(<20\%\)), 13 patients (54%) exhibited a significant response during inhalation of iloprost (e.g., a decrease of the pulmonary vascular resistance by \(>20\%\); Fig. 1C).

**Time course.** The effects of NO were evident within 2 to 5 min after the beginning of the inhalation and lasted only for a couple of minutes after the supply was stopped (data not shown). The effects of iloprost also became evident within 2 to 5 min after the inhalation was started and reached a maximum at cumulative doses between 14 and 17 \(\mu g\), which, in our setting, were attained within 12 to 15 min. The maximum effect was maintained for 5 to 30 min and then began to wane. Sixty minutes after the end of inhalation, there was no longer a significant change in the pulmonary vascular resistance. The data of a subset of 20 patients for whom a complete 1-h monitoring was available are shown in Figure 2.

**Side effects.** No severe complications related to catheter testing or drug administration occurred during this study. Inhalation of NO and of iloprost was generally well tolerated. No patient experienced any side effect during inhalation of NO, but five patients developed minor headache and a facial flush while inhaling iloprost. These side effects did not lead to premature termination of the inhalation and ceased a few minutes after the inhalation was ended. One patient described mild jaw pain immediately after inhalation of iloprost, which also ceased after a few minutes. Gastrointestinal discomfort was not observed. In addition, there was no evidence of rebound pulmonary hypertension after administration of NO or iloprost.

**DISCUSSION**

In this study, we compared the acute effects of aerosolized iloprost and inhaled NO in patients with PPH. Notably, iloprost caused a significantly greater decline in pulmonary arterial pressure and pulmonary vascular resistance than NO. In addition to its hemodynamic profile, aerosolized iloprost, in contrast to inhaled NO, also exerted beneficial effects on arterial oxygenation, which probably reflected the more potent effects of iloprost on the pulmonary vascular bed and the more pronounced increase of mixed-venous oxygen saturation.

The more potent acute effect of iloprost on pulmonary vascular resistance was reflected not only by a more pronounced decline of pulmonary artery pressure but also by a more prominent increase in CO when compared with NO. Since iloprost uniformly exhibited such effects on CO, even in patients in whom both NO and iloprost caused a similar decline of pulmonary artery pressure, we speculate that some degree of systemic vasodilation in response to iloprost inhalation could have led to activation of the baroreceptor reflex, which may have resulted in an indirect positive inotropic effect due to increased sympathetic nerve activity. A direct positive inotropic action of iloprost could be an alternative explanation because a prostanoid-mediated increase of cyclic AMP in cardiomyocytes has been shown to exert positive inotropic effects in experimental models (20,21). However, at this time, it is unclear whether PG\(_I\)\(_2\) receptors are expressed on human cardiomyocytes.

Unexpectedly, NO caused an increase in pulmonary artery pressure and pulmonary vascular resistance in 10 out of 35 (29%) and 6 out of 35 (17%), respectively, of our patients. This observation concurs with a report from Sitbon et al. (10), who reported an increase of pulmonary artery pressure and pulmonary vascular resistance in 8 out of 35 (23%) and 11 out of 35 (31%) of their patients, respectively, while using a comparable concentration of NO. The mechanisms by which NO may cause an increase in pulmonary vascular resistance remain obscure. Voelkel et al. (22) have shown that under certain experimental circumstances, for example, in the presence of hemolysate, NO may become a potent pulmonary vasoconstrictor, but again, the underlying mechanisms are still unknown. By contrast to inhaled NO, aerosolized iloprost caused a decline in pulmonary artery pressure and pulmonary vascular resistance in all of our patients (except for one patient in whom the pulmonary artery pressure remained unchanged).

The acute hemodynamic effects of aerosolized iloprost on pulmonary artery pressure, pulmonary vascular resistance and CO in PPH patients compared quite well with pub-
lished effects of acute intravenous PG12 (4,10,16,23). However, a decline in systemic blood pressure was a potential side effect in patients receiving intravenous PG12, and some patients with advanced right heart failure may not tolerate even lowest doses of intravenous PG12 (24). By contrast, clinically relevant systemic hypotension was not observed in any of our patients receiving aerosolized iloprost.

The action of aerosolized iloprost was relatively short-lived and vanished almost completely within 1 h after inhalation (Fig. 2). This observation was surprising with respect to the demonstration of sustained benefits of intermittent delivery of aerosolized iloprost as described by Olschewski and coworkers (16,24). There is evidence that the long-term effects of PG12 might not be related simply to vasodilation but to other, yet unknown, mechanisms affecting pulmonary vascular remodeling (4,7,25,26). It seems possible that some of these ill-defined effects of prostanoids on the pulmonary vasculature in pulmonary hypertension do not require continuous administration (27).

Our study has several limitations. First, NO was always given before iloprost, and although we ensured that the hemodynamics had returned to baseline before iloprost was administered, we cannot fully exclude a conditioning or priming effect of pretreatment with NO. Furthermore, the concentration of 40 ppm NO used in our study may not have caused maximum vasodilation in all patients. However, recent investigations have shown that maximum effects on pulmonary artery pressure can be achieved with NO concentrations between 10 and 20 ppm and that higher concentrations of NO do not augment the vasodilatory action (10).

In summary, aerosolized iloprost exhibited a favorable hemodynamic response during acute drug testing in our PPH patients: pulmonary artery pressure and pulmonary vascular resistance decreased, CO and arterial PO2 increased, and systemic blood pressure remained stable. Compared with the acute effects of inhaled NO, aerosolized iloprost—at least at the doses used in this study—was significantly more potent in reducing pulmonary artery pressure and pulmonary vascular resistance and also caused a significantly greater increase in CO. Moreover, aerosolized iloprost was well tolerated, and no major side effects were observed.

**APPENDIX**

Members of the German PPH study group are as follows: Werner Seeger, MD, Horst Olschewski, MD, Friedrich Grimminger, MD, H.A. Ghofrani, MD, Thomas Schmehl, PhD, Saskia Diehl, F. Rohlfing, Justus Liebig University Giessen; Marius M. Hoeper, MD, Michael Hamm, MD, Jost Niedermeyer, MD, Helmut Fabel, MD, Medizinische Hochschule Hannover; Heinrike Wilkens, MD, Andreas Eichler, MD, Gerd Sybrecht, MD, University of the Saarland, Homburg; Joerg Winkler, MD, Joachim Schauer, MD, University of Leipzig; Mathias M. Borst, MD, F.-Joachim Meyer, MD, Wolfgang Kühler, MD, FRCP, Ruprecht-Karls-University of Heidelberg; Friedrich Klüppelberg, MD, Volker Schulz, MD, Thoraxklinik Heidelberg; M. Behr, MD, Claus Vogelmeier, MD, Klinikum Großhadern, Munich; Heinrich Worth, University Hospital of Fürth; Germany.

**Acknowledgment**

The authors wish to thank Wolfgang Pabst for his support with the statistical analysis.

**Reprint requests and correspondence:** Dr. Marius M. Hoeper, Department of Pulmonary Medicine, Hannover Medical School, 30623 Hannover, Germany. E-mail: KMHoeper@AOL.com.

**REFERENCES**

17. Sinzinger H. Prostacyclin and Its Stable Analogue Iloprost. Gry-
20. Mohan P, Brutsaert DL, Sys SU. Myocardial performance is modu-
lated by interaction of cardiac endothelium derived nitric oxide and
21. Rebsamen MC, Church DJ, Morabito D, Vallotton MB, Lang U.
Role of cAMP and calcium influx in endothelin-1-induced ANP
22. Voelkel NF, Lobel K, Westcott JY, Burke TJ. Nitric oxide-related
23. Warren JB, Higenbottam TW. Caution with the use of inhaled nitric
circulatory shock in severe primary pulmonary hypertension (PPH)
25. Magnani M, Galie N. Prostacyclin in primary pulmonary hyperten-
vascular endothelial growth factor in a human monocytic cell line
and in rat lungs via cAMP. Am J Respir Cell Mol Biol 1997;17:748–56.
27. Niewierowicz I, Eskilsson J, Scheja A, Akesson A. Intermittent
iloprost infusion therapy for pulmonary hypertension in scleroder-