Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease

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Background—Increased pulmonary vascular resistance (PVR) because of congenital heart disease (CHD) may be caused by a dysfunction in endogenous pulmonary endothelial nitric oxide (NO) production. In other forms of pulmonary vascular disease with increased PVR, an elevated activity of a phosphodiesterase type 5 (PDE-5), responsible for the degradation of cyclic guanidine monophosphate (cGMP), the second messenger of endothelially produced NO, has been demonstrated. This study compares the effects of inhaled NO before and after the specific inhibition of the PDE-5 by intravenous sildenafil (Viagra™) in pre- and postoperative children with increased PVR because of CHD.

Methods and Results—12 children with congenital heart disease (age 0.2 to 15.7 years, median 2.4 years) and increased mean pulmonary arterial pressure, and 12 postoperative children (age 0.11 to 0.65 years, median 0.32 years) with increased PVR (8.3 ± 1.0 Wood Units*m²) were studied during cardiac catheterization (“cath laboratory”), or within 2 hours after return from cardiac surgery (“post op”), respectively. All were sedated, tracheally intubated and paralyzed. During alveolar hyperoxygenation (FIO₂ = 0.65), the effects of inhaled NO (20 ppm) were compared before and after the stepwise infusion of sildenafil (“cath laboratory”, 1 mg/kg; post op, 0.25 mg/kg).

Intravenous sildenafil more effectively reduced PVR than NO (11.5% versus 4.3% in the “cath laboratory” patient group, P < 0.05, and 25.8% versus 14.6% in the post op patient group, P = 0.09). The increase in cGMP in response to NO was potentiated (2- to 2.4-fold) by PDE-5 inhibition. While the vasodilating effects of sildenafil showed pulmonary selectivity, its infusion was associated with increased intrapulmonary shunting in the postoperative patients (Qs/Qt = 16.5 ± 4.7% to 25.5 ± 18.2%, P = 0.04).

Conclusions—Intravenous sildenafil is as effective as inhaled NO as a pulmonary vasodilator in children with congenital heart disease. Although clinically insignificant in this study, increased intrapulmonary shunting with sildenafil may be disadvantageous in some patients after CHD surgery. (Circulation. 2003;108[suppl II]:II-167-II-173.)

Key Words: heart defects ■ congenital ■ heart surgery ■ pulmonary circulation ■ hypertension ■ pulmonary nitric oxide ■ sildenafil

It has been shown that increased pulmonary vascular resistance in many forms of pulmonary hypertension (PHT) is associated with pulmonary endothelial dysfunction (PED), defined as failure of the pulmonary endothelium to produce adequate amounts of endogenous nitric oxide (NO). This has also been demonstrated in children with congenital heart disease preoperatively, and is amplified by cardiopulmonary bypass (CPB) surgery in the postoperative child. For these reasons, administration of exogenous inhaled nitric oxide has become part of the preoperative assessment of patients undergoing formal assessment of pulmonary vasoactivity during cardiac catheterization before treatment, and as a treatment for postoperative pulmonary hypertension.

Inhaled NO has some disadvantages, however. Some patients fail to respond to nitric oxide inhalation. Alternatively, responders to longterm NO therapy may develop severe, life-threatening, rebound pulmonary hypertension on withdrawal of nitric oxide. We have recently shown that by enhancement of the NO-arginine pathway, ie, by providing the substrate for NO-production (L-arginine) and stimulating the enzyme responsible for NO-formation (substance P), that there is almost no PED in preoperative patients, and that it is possible to restore the pulmonary endothelial vasodilating function to a large degree in most postoperative patients.

Cyclic guanosine-monophosphate (c-GMP) is produced by the interaction of NO with guanidine cyclase, and is a final messenger for vascular smooth muscle relaxation. It is metabolized by a phosphodiesterase (PDE 5) which is the predominant PDE in normal lung, and which may be upregulated in patients with primary pulmonary hypertension, and

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after cardiopulmonary bypass,\textsuperscript{6} causing an increased turnover of cGMP.

The inhibition of PDE5 is therefore, a logical step to increase the bioavailability of cGMP and thus support endogenous vasodilation. Previous studies in animal models of pulmonary hypertension using the PDE-inhibitors zaprinast or rolipram have confirmed this as a valid approach, but the data are less robust in humans treated with oral dipyridamole,\textsuperscript{7} and intravenous enoximone.\textsuperscript{8} This is because both dipyridamole and enoximone have low selectivity to the PDE5 present in the lungs, and their action is complicated by important systemic vasodilator effects.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5).\textsuperscript{9} The intravenous preparation of sildenafil makes it the only titratable PDE5 inhibitor available so far. However, besides anecdotal reports from a few patients,\textsuperscript{10} there are no systematic data available on the effects of sildenafil in the pulmonary circulation in children.

Thus, in this study, we compared the effects of inhaled nitric oxide with the effects of intravenous sildenafil, as well as possible synergistic action of their combination, in both pre- and postoperative children with congenital heart disease.

### Materials and Methods

#### Patients

The study was approved by our Hospital Research Ethics Committee, and written informed consent was obtained from the parents of each child. The patients (Table 1) examined during routine cardiac catheterization had their study at the end of the diagnostic element. Postoperative patients were studied within 2 hours after return from surgery. All were sedated, paralyzed using vecuronium, and sedated with propofol, ketamine, and midazolam. Postoperative catecholaminergic support with low-dose infusion of dopamine was provided, while other intravenous NO-donors or PDE-inhibitors were excluded. All were mechanically ventilated using a cuffed endotracheal tube (Mallinckrodt, Athlone, Ireland) to exclude any respiratory gas leaks. For the duration of the study protocol, the cuff of the endotracheal tube was inflated with a pressure below the systemic diastolic blood pressure, and continuous monitoring of hemodynamic pressures, surface ECG, pulse oximetry, and end-tidal carbon dioxide concentration (see below) was also performed.

#### Hemodynamic Measurements and Determination of Oxygen Consumption

Systemic arterial and pulmonary arterial, as well as right and left atrial pressures (directly during catheterization or with intraoperatively placed pressure lines) were measured.

Endtidal CO\textsubscript{2} (etCO\textsubscript{2}) and systemic oxygen consumption ($\dot{O}_2$) were continuously determined using respiratory mass spectrometry by the mixed expirate inert gas dilution method\textsuperscript{11} with our previously described modification\textsuperscript{5} for use in ventilated patients. Special care was taken to detect and exclude any air leaks or carbon dioxide contamination of the monitoring and ventilatory circuits. The mass spectrometer was calibrated directly before the study and then every 30 minutes to exclude any measurement drift.

#### Study Protocol

The study protocol was commenced (a) after the necessary diagnostic steps during the cardiac catheterization, but before any angiography; (b) within 2 hours after return from the operation theater. After measurements at baseline ($F_O$\textsubscript{2} 0.21 to 0.25 or that found on return from the operating room = “base”); $F_O$\textsubscript{2} was increased to 0.65 (“O\textsubscript{2} 1”), an inspiratory oxygen concentration which has been shown to be low enough to allow stable oxygen consumption measurements while being high enough to provide alveolar hyperoxia and remained so until the end of the study (alveolar hyperoxegenation). The effect of additional inhaled NO at 20 ppm for 10 minutes was then recorded. After a second oxygen only step for 10 minutes, the effects of infused sildenafil (“cath laboratory”: 0.33 mg/kg and 0.66 mg in 10 minutes; post op: 0.025, 0.10, and 0.25 mg/kg, each in 10 to 15 minutes steps) were compared. Finally, after the complete infusion of sildenafil, inhaled NO (20 ppm) was added again for 10 minutes. After the end of the study protocol, with all monitoring in place, the NO was stopped, the oxygen reduced, and the children observed for a further 30 minutes.

#### Blood Gases and Determination of Sildenafil and cGMP-Levels

Blood samples were taken from the pulmonary artery (prepulmonary) and the left atrium (postpulmonary). The partial pressures for oxygen and carbon dioxide and hemoglobin saturation were measured by the spectral absorption method (Chiron 270 CO-oximeter). Blood samples were then collected in heparinized polypropylene tubes and centrifuged after completion of the study for 10 minutes at

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arterialized (pulmonary venous) and venous (pulmonary arterial) was derived using the Fick principle as \( \frac{O_2}{AVD_O2} \). Pulmonary vascular resistance (PVR, \( \text{WU/m}^2 \)) was derived from the transpulmonary pressure gradient \( P_{A}CO_2 - P_{E}CO_2 \) divided by cardiac output (Qc/Qt). Qs/Qt was calculated as \( \frac{Qs}{Qt} \).

### Hemodynamic Parameters

#### Cath Laboratory

Mean pulmonary artery pressure remained unchanged until the infusion of sildenafil, falling from 42±16 to 38±14 mm Hg (\( P=0.004 \); Table 2). Pulmonary vascular resistance index decreased with hyperoxia (7.2±4.1 to 5.6±3.3 WU*BSA, \( P=0.010 \)). There was a non-significant fall with inhaled nitric oxide (5.6±3.2 to 5.3±3.2 WU*BSA, \( P=0.34 \)), but a significant reduction occurred with infused sildenafil (5.5±3.1 to 4.5±2.3, \( P=0.011 \); Figure 1). The pulmonary vasodilating capability of intravenous sildenafil was higher than that of inhaled nitric oxide (11.5% versus 4.3% PVRi reduction, \( P<0.05 \); Figure 2), which was not augmented by the additional combination with inhaled nitric oxide.

#### Post Op

Mean systemic blood pressure fell in response to the infusion of sildenafil (a fall of 7.3±2.5 mm Hg, \( P<0.01 \); Figure 3), however, these changes in each patient remained clinically nonsignificant. Cardiac index increased in response to hyperoxia and remained unchanged throughout the study protocol (Table 2). PVRi was significantly lowered by hyperoxia (28±19%, \( P<0.001 \)). The effect of inhaled nitric oxide before PDE5-blockade was non-significant. Intravenous sildenafil alone lowered PVRi, mainly due to a fall in pulmonary artery pressure (Figure 2), which tended to be more than that with inhaled NO alone (25.8% versus 14.6% PVRi reduction, \( P=0.09 \)). The addition of inhNO after PDE5-blockade did not cause a significant augmentation of the effects of sildenafil alone. Although iv sildenafil lowered

### Results

#### Patients

There were 12 children with congenital heart disease (age 0.2 to 15.7 years, median 2.4 years, cath laboratory patient group) and increased mean pulmonary arterial pressure, and 12 postoperative children (age 0.11 to 0.65 years, median 0.32 years, post op patient group) with increased PVR (7.2±4.1 WU/m² in the cath laboratory group, and 8.3±1.0 WU/m² in the post op patient group) were included (Table 1).

### Statistical Methods

All results are presented as mean values±SEM. Repeated measures of analysis of variance (MANOVA) were used to look for differences in the measurements of all study conditions. If differences were found, then the Bonferroni multiple comparisons procedure was used to determine where differences existed. A probability value of <0.05 was considered significant.

### Calculated Variables

Cardiac output and vascular resistances. The arterio-venous oxygen content difference (avDO2 [ml/L]) was calculated, and cardiac output was derived using the Fick principle as \( \frac{O_2}{AVD_O2} \). Pulmonary vascular resistance (PVR, \( \text{mm Hg/(L/min)} \)) and PVR-index (PVRI, \( \text{mm Hg/(L/min)*BSA} \)) was derived from the transpulmonary pressure gradient \( \Delta P_{PA} \) [\( \text{mm Hg} \)] using standard formula and reported in Wood Units indexed to body surface area (WU/m²).

Intrapulmonary shunting (Qs/Qt) and alveolar deadspace ventilation (VD/VT). Qs/Qt was calculated as \( \frac{Qs}{Qt}=(C_c-C_v)/(C_c-C_a) \), where \( C_c \) is ideal end-capillary O2-content, and \( C_a \) and \( C_v \) are the arterialized (pulmonary venous) and venous (pulmonary arterial) O2-contents. VD/VT was calculated as \( \frac{VD}{VT}=(P_\text{CO}_2-P_\text{CO}_2)\text{eCO}_2/P_\text{CO}_2 \), where \( P_\text{CO}_2\text{eCO}_2 \) and \( P_\text{CO}_2 \) are mixed expired CO2 and \( CO_2 \) in the lung (\( CO_2 \))

### Table 2: Hemodynamic Data of Patient Groups

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4000 rpm; the supernatant plasma was pipetted into crew capped polypropylene tubes and stored at −20C, within 50 minutes of blood sample collection. Plasma samples were assayed for sildenafil using a previously validated high performance liquid chromatography (HPLC) technique with detection and quantification by atmospheric pressure chemical ionization mass spectroscopy. For cGMP-levels, plasma samples were assayed by Hayleton, UK, Harrogate HG3 1PY, UK, using a commercially available radioimmunoassay (Du Pont Speciality Diagnostics). The calibration range for the assay was 0.025 to 5.0 pml/mL.
systemic blood pressure, pulmonary selectivity (PVRI/SVRI-ratio, Table 2) was maintained.

Gas-Exchange and Metabolic Parameters
Patients were ventilated with 200 to 350 mL/(kgm˙·min), so that endtidal pCO₂ was 4.5 to 5.5 kPa throughout the protocol, with arterial blood pH 7.4. Oxygen uptake (O₂) remained unchanged throughout the study protocols [range, 5.8 to 7.2 mL/(kgm˙·min)].

Cath Laboratory
In the preoperative patients, arterial blood pO₂ increased from 15.4±5.7 to 42.1±4.3 with hyperoxia and did not change significantly during the further steps of the protocol. However, there was a trend to increased intrapulmonary shunting (Qs/Qt) during hyperoxia (14.7±15.2% to 20.5±18.5%, P=0.16), remaining unchanged during the further steps of the protocol. Physiological dead-space ventilation (VD/VT) remained unchanged throughout.

Post Op
In the postoperative patients, intrapulmonary shunting increased when iv. sildenafil was started and was significantly higher after the last sildenafil infusion step (16.5±4.7% in hyperoxia to 25.5±18.2% after sildenafil infusion, P=0.04) (Figure 4). However, no patient experienced significant hypoxemia. Physiological dead-space ventilation (VD/VT) remained unchanged throughout.

Sildenafil and cGMP-Levels
Cath Laboratory
Sildenafil infused at 0.33 mg/kg and 0.66 mg/kg achieved plasma levels 946±333 ng/mL and 2198±979 ng/mL, respectively. Baseline cGMP-levels were 29±23 pmol/mL. Inhaled NO, and the infusion of sildenafil, led to a nonsignificant increase of plasma cGMP-levels (to 39±26 pmol/mL and 44±18 pmol/mL), but rose significantly with inhaled NO after PDE-5 blockade (P<0.001, Figure 5, Table 3).

Post Op
The stepwise infusion of sildenafil resulted in plasma sildenafil levels of 26±10 ng/mL, 96±26 ng/mL, and 226±49 ng/mL, and these were correlated with a progressive fall in PVRI (r=0.87, P<0.01). There was no increase in cGMP during inhaled NO administration before PDE-5-blockade. Intravenous Sildenafil led to an increase in cGMP (P<0.05), and to a more pronounced response to inhaled NO (P<0.01; Table 3).

Discussion
This is the first study systematically assessing the effects of intravenous sildenafil in children with congenital heart disease. It shows that intravenous sildenafil may be equal or superior to a usual therapeutic dose of inhaled nitric oxide in reducing the elevated pulmonary vascular resistance in children with congenital heart disease both during routine cardiac catheterization and after open-heart surgery. In keeping with its systemic administration and its relative nonselectivity, these effects were associated with a significant increase in intrapulmonary shunting and a clinically nonsignificant fall in arterial blood pressure.

Figure 1. Pulmonary vascular resistance index (Wood Units · m²) during hyperoxegenation (FiO₂=0.65), and additional inhalation of nitric oxide (NO, 20 ppm) before and after the administration of infused sildenafil (S, cath laboratory patient group: 0.33 and 0.66 mg/kg; post-op patient group: 0.025, 0.10, and 0.25 mg/kg).

Figure 2. Percentage of reduction in pulmonary vascular resistance: cath laboratory patients, gray boxes; post-op patients, black boxes. (a) caused by the inhalation of nitric oxide (NO, 20 ppm), (b) after the administration of infused sildenafil (Sild., cath laboratory patient group: 0.33 and 0.66 mg/kg; post-op patient group: 0.025, 0.10, and 0.25 mg/kg), and (c) the combination of both.
Clinical Impact of Increased PVR in Children with Congenital Heart Disease

Increased PVR is a universal finding after cardiopulmonary bypass. While the clinical impact of pre- and postoperative PHT has become considerably less threatening during the last decade, there are some patients who develop marked postoperative PHT associated with hemodynamic compromise. Furthermore, subclinical elevation of PVR may be associated with prolonged postoperative recovery. Treatment with inhaled NO has become standard of care in most units, but there are nonresponders, and rebound PHT on withdrawal can be difficult to manage. Alternative strategies to lower PVR, may therefore have a therapeutic role.

Hyperoxia and Artificial Ventilation as NO-Independent Manipulation of PVR

Our finding that oxygen is a powerful and important pulmonary vasodilator confirms many other studies in pre- and postoperative patients and in different disease entities. This is because of both a direct effect on pulmonary vascular smooth muscle, and also a reversal of hypoxic vasoconstriction secondary to ‘post-pump’ parenchymal lung changes in the postoperative group. Indeed, the hyperoxia was used in our patients to avoid the confounding effects of alveolar hypoxia, inducing a raised PVR, independent of PED.

Intravenous Sildenafil Compared with Inhaled NO as a Specific Pulmonary Vasodilator

We have demonstrated the effects of intravenous sildenafil in 2 contemporary groups of patients with congenital heart disease. In the cath laboratory patients, intravenous sildenafil was more potent then a standard clinical dose of inhaled nitric oxide. While still effective in post op patients, the overall effect of inhaled NO and sildenafil was not significantly different. In contrast to previous animal studies, we found no significant effects on intrapulmonary shunting in our cath laboratory patients, but this was clearly an important issue in postoperative mechanically ventilated patients. In the presence of alveolar hyperoxia, the fall in arterial pO2 was statistically significant, but was not associated with clinically relevant hypoxemia. This is presumably related to vasodilation of pulmonary arterioles supplying non-ventilated areas of lung, a well-described complication of intravenous, non-selective pulmonary vasodilation. It is in contrast to inhaled NO where its effect is localized only to adequately ventilated areas of lung. It should be emphasized, however, that none of our patients had significant residual cyanosis, or overt lung parenchymal abnormalities (atelectasis/pneumonia) and sildenafil must be used cautiously in such patients.

While in a previous study, we demonstrated in preoperative children with congenital heart disease an almost complete fall
of mildly increased PVRI to normal with hyperoxia alone, in other studies with more severely diseased and older patients, PVRI fell with oxygen and again with 50 to 80 ppm NO. Our patients had moderately increased PVRI which failed to respond to 20 ppm of NO. It is possible that a higher dose of inhaled NO would have produced a more marked effect. Some studies have suggested a flat dose response curve to NO above 2 ppm, while others have suggested continued effects up to 80 ppm. The dose used in this study was chosen to be relevant to the highest dose used clinically. Higher doses, applied continuously, may be associated with methemoglobinemia, and are rarely used. This is a particular issue in postoperative patients. Again, the fall in PVR with inhaled NO just failed to reach significance (P=0.054), but the fall with sildenafil was more marked, and significant. Again, this study was not designed to examine a dose-response relationship to inhaled NO, and we chose a clinically relevant dose, for comparison.

Blood Plasma Levels of Sildenafil and cGMP

The resulting levels of sildenafil in our patients correspond to those of previous studies: in a human study, 20, 40, and 80 mg sildenafil were infused into 8 healthy 60 to 90 kg volunteers. The resulting sildenafil plasma levels were 331, 883, and 1822 ng/mL, respectively, thus comparable to our 1 mg/kg infusion. This is approximately twofold of that expected with oral dosing. In all those studies, both the infusion and oral administration were tolerated hemodynamically without significant side effects.

The effect of sildenafil on cGMP has been demonstrated in only 2 patients with congenital heart disease previously. cGMP rose from 12 to 28, and 19 to 30 pmol/mL in 2 patients treated with oral sildenafil (0.33 mg/kg) in a description of its use to suppress rebound PHT after prolonged NO-therapy. In a larger study of adult patients with mostly primary PHT, there was a potentiation of cGMP-levels in response to inhaled NO after the administration of oral sildenafil.

Similarly, in both pre- and postoperative patients of this study, there was an association between the increase in plasma cGMP-level and the fall in PVRI. This increase in plasma cGMP in response to inhaled nitric oxide was potentiated after the infusion of intravenous sildenafil. However, in the individual patient, neither in the cath laboratory nor in the post op group did the percentage fall in PVRI correlate with the percentage increase in plasma cGMP. The lack of response to a significant rise in cGMP, when inhaled NO was added to sildenafil in the pre- and postoperative patients, suggests that the smooth muscle cell can be ‘saturated’ with cGMP. Our data do not support the use of combination therapy in these patients.

Conclusion

We have shown that in children with raised pulmonary vascular resistance due to congenital heart disease, infused sildenafil lowers pulmonary vascular resistance. The pulmonary vasodilation with sildenafil was associated with an increase of plasma cGMP. These findings suggest that an overactivity of cGMP-degrading phosphodiesterase-5, together with a decrease in endogenous NO production, may contribute to the increased pulmonary vascular resistance in these patients. The increased intrapulmonary shunting seen in postoperative patients may limit its use, and future clinical studies in this group of patients must take account of this potential confounding effect.

References


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