Does prostacyclin enhance the selective pulmonary vasodilator effect of oxygen in children with congenital heart disease?


ABSTRACT We have obtained dose-response curves for the effects of prostacyclin on the pulmonary and systemic circulations in 20 children (median age 3 years) with pulmonary hypertension complicating congenital heart disease. Results were obtained with the children breathing both air and 100% oxygen. Under both sets of conditions, remote respiratory mass spectrometry was used to measure oxygen consumption and hence cardiac output by the direct Fick principle. When the subjects breathed air, prostacyclin caused a dose-dependent fall in pulmonary vascular resistance (measured in mm Hg \cdot liter^{-1} \cdot min \cdot m^2) (11.12 to 8.07, standard error of difference [SED] = 0.5, p < .01). The level of the pulmonary vascular resistance when the subjects breathed air during the infusion of 20 ng/kg/min prostacyclin was not significantly different from that found when they breathed 100% oxygen and did not receive the drug (8.67 vs 8.93, SED = 0.55, p = NS). When infused while the subjects breathed 100% oxygen, prostacyclin caused additional dose-dependent pulmonary vasodilation (pulmonary vascular resistance 8.93 to 7.23, SED = 0.3, p < .01). Unlike 100% oxygen, prostacyclin was not selective, and caused tachycardia and systemic hypotension at the higher doses. These results suggest that in children with congenital heart disease 100% oxygen does not maximally vasodilate the pulmonary circulation, and further pulmonary vasodilation at the higher doses can be obtained with a blood-borne agent.

Circulation 74, No. 1, 135-144, 1986.

Oxygen is a powerful and selective pulmonary vasodilator, but long-term administration is inconvenient and may cause lung toxicity when high concentrations are breathed for even a short time. Many drugs have been tested in an attempt to find an agent that reduces pulmonary vascular resistance (PVR) while either constricting or at least not dilating the systemic circulation. Marked systemic venodilatation may result in a sudden drop in cardiac output due to a reduced systemic venous return even in the presence of a relatively less marked decrease in arterial resistance. Systemic hypotension, alone or with a fall in cardiac output, may also be dangerous in patients with severe pulmonary vascular disease because it reduces myocardial perfusion and may thus account for many of the deaths associated with pulmonary vasodilator therapy.

Prostacyclin (PGI₂) is an arachidonic acid metabo-

tite that is continuously secreted by vascular endothelial cells. Almost alone among prostaglandins, it is not metabolized by the lungs. Its physiologic role is not clear. It was initially thought to be a circulating hormone, but concentrations of PGI₂ in peripheral blood are very low. It has many putative local effects on blood vessels, platelets, and their interactions. PGI₂ was thought to be a highly selective pulmonary vasodilator on the basis of animal experiments and studies in infants with pulmonary hypertension. It has been suggested that it is a more selective pulmonary vasodilator than other prostaglandins. It may mediate the action on the pulmonary circulation of drugs such as hydralazine. However, studies in adults have shown that PGI₂ is a potent systemic vasodilator implying that there may be age- and species-related differences in its effects. We have therefore studied the effects of PGI₂ in 20 children with congenital heart disease, both preoperatively and in the context of postoperative pulmonary hypertensive crises.

Methods

We studied 20 patients with pulmonary hypertension complicating congenital heart disease who required evaluation for post-
sible pulmonary vascular disease. Details on the patients and their diagnoses are given in table 1. In no patient was the arterial duct patent at the time of the study. Fifteen patients were studied preoperatively in the catheter laboratory and five (patients 3, 7, 12, 17, and 19) were studied in the intensive care unit after surgery to optimize postoperative pulmonary vasodilator therapy. No patient had clinical or radiographic evidence of pulmonary edema or coexisting lung disease.

We obtained dose-response curves for the effects of PGI2 on the pulmonary and systemic circulations in patients breathing 100% oxygen and either air or the lowest inspired oxygen tension (FiO2) considered safe by the attending physician (patients 7, 12, and 17). We measured pressures, flows, and resistances in the pulmonary and systemic circulations, and also heart rate at each dose level of PGI2. Details of the protocol and measurement techniques follow. The protocol was approved by the Brompton Hospital Ethics Committee and informed consent was obtained in each case, usually from the parents. PGI2 was synthesized by Upjohn and formulated and supplied by the Wellcome Foundation Limited.

All the patients were premedicated with trimethapine, papaverine, and either atropine or scopolamine. They were anesthetized with alfalone-alphadoline acetate (Althesin) by continuous intravenous infusion and paralyzed with pancuronium bromide. A closely fitting endotracheal tube was passed. It was then checked for leaks by examination for raised carbon dioxide tension in the mouth and nose. Any leak detected was eliminated by changing the tube or by packing the pharynx. Stability and adequacy of ventilation were checked throughout the study by continuous monitoring of expired gases by remote respiratory mass spectrometry. End-tidal partial pressure of carbon dioxide (PcO2) was required to be less than 5.3 kPa and to remain within 0.5 kPa of baseline. In all cases systemic arterial PcO2 was also less than 5.3 kPa, with pH greater than 7.36. Fluid-filled catheters were positioned in the aorta and pulmonary artery. The patients initially breathed air or the lowest FiO2 considered safe (patients 7, 12, and 17, FiO2 of 0.55, 0.50, and 0.30, respectively).

After any necessary diagnostic procedure (except angiography), measurements were made of (1) end-tidal gases and oxygen consumption (VO2), by remote respiratory mass spectrometry, and (2) systemic (AoP) and pulmonary arterial pressure (PAP) and heart rate. VO2 was measured over at least 3 min, during which time samples of blood were simultaneously drawn from each catheter. If feasible, a second pair of blood samples was obtained. These baseline measurements having been made, an intravenous infusion of PGI2 was commenced at a dose of 5 ng/kg/min. After 5 min of the infusion, all measurements were repeated. The dose was then increased in increments of 5 ng/kg/min until a dose of 20 ng/kg/min was reached. Measurements were made after 5 min at each dose level. We would have stopped the infusion if mean AoP had fallen by more than 20 mm Hg, but this was never necessary. At the end of this series, the inspirate was changed to 100% oxygen. Comparability of ventilation and adequacy of nitrogen washout were checked by monitoring the expired gases. Mixed expired nitrogen was required to be less than 1%, and end-tidal Pco2 was required to remain stable as defined above. During the changeover period, the infusion of PGI2 was continued. After 10 min of 100% oxygen, measurements were made and the dose of PGI2

### Table 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>PAP (mm Hg)</th>
<th>Qp (l/min/m²)</th>
<th>PVR (mm Hg l⁻¹ min⁻¹ m⁻²)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Lowest</td>
<td>Baseline</td>
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<tr>
<td>1</td>
<td>12</td>
<td>PDA/AS/COARC</td>
<td>130</td>
<td>96</td>
<td>3.34</td>
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<tr>
<td>2</td>
<td>8</td>
<td>VSD</td>
<td>100</td>
<td>94</td>
<td>3.93</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>AVSD/PAB/DS</td>
<td>39</td>
<td>25</td>
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<td>ASD</td>
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<tr>
<td>7</td>
<td>2/12</td>
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<td>14</td>
<td>0.56</td>
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<tr>
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<td>3</td>
<td>VSD/TA/DS</td>
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<tr>
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<tr>
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<td>4</td>
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<tr>
<td>11</td>
<td>6</td>
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<td>41</td>
<td>7.15</td>
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<td>1</td>
<td>VSD</td>
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<td>5.26</td>
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<tr>
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<td>7/12</td>
<td>VSD/DS</td>
<td>41</td>
<td>32</td>
<td>6.40</td>
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<tr>
<td>14</td>
<td>6/52</td>
<td>ASD/VSD/PDA/UPA</td>
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<td>25</td>
<td>3.34</td>
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<tr>
<td>15</td>
<td>7</td>
<td>VSD/PDA</td>
<td>32</td>
<td>15</td>
<td>5.24</td>
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<tr>
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<td>5/12</td>
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<td>3.64</td>
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<tr>
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<td>3/12</td>
<td>PS/PAPVD</td>
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<td>8.16</td>
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<tr>
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<td>13.95</td>
</tr>
<tr>
<td>19</td>
<td>10/12</td>
<td>VSD/DS</td>
<td>28</td>
<td>21</td>
<td>10.34</td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>ASD/MR/DS</td>
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<td>25</td>
<td>9.06</td>
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</tbody>
</table>

Qp = pulmonary blood flow; AS = aortic stenosis; ASD = atrial septal defect; AVSD = atrioventricular septal defect; COARC = coarctation; DS = Down’s syndrome; MR = mitral regurgitation; PAB = pulmonary artery banding; PAPVD = partial anomalous pulmonary venous drainage; PDA = patency of the arterial duct (closed surgically prior to study in all cases); PS = pulmonary stenosis; TA = truncus arteriosus; UPA = unilateral absence of pulmonary artery; VSD = ventricular septal defect.
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was reduced stepwise in decrements of 5 ng/kg/min. The measurements were repeated at the end of each 5 min period, with the final measurements being made 5 min after stopping the infusion.

Calculation of PVR requires measurement of pulmonary blood flow and the pressure drop across the pulmonary circulation. Pulmonary blood flow was measured by the direct Fick principle.29 With the patient breathing air or an FiO2 of less than 0.6, VO2 and CO2 production were measured directly, and the respiratory exchange ratio (RER) was calculated at each dose of PG12. When the patients breathed 100% oxygen, VO2 was calculated from measured CO2 production and the RER, which was assumed to be that at the corresponding dose of PG12 in patients on air.

Detailed descriptions of these protocols, including the development of remote respiratory mass spectrometry to measure metabolic gas exchange, have been published elsewhere.30-33 Blood samples were taken into heparinized 1 ml syringes that were checked for the absence of gas bubbles, capped, stored in a vacuum flask filled with crushed ice, and analyzed with as little delay as possible (and always within 10 min) on an automatic pH and blood gas electrode unit (Corning 165). The effects of any possible delay on measured blood oxygen content have been investigated and shown to be minor.33 The oxygen content of each sample was calculated with the use of the data of Kelman34 and assuming the solubility of free oxygen in blood to be 0.003 ml/100 ml/mm Hg. The reasons for the use of calculation rather than direct measurement and the validity of the calculation in chronically hypoxic patients have been discussed elsewhere.33 The same data were used to calculate the oxygen content of pulmonary end-capillary blood with the use of the Po2 predicted from measurements of the end-tidal PCO2 and the alveolar air equation. The choice of blood samples that were used for the calculations in the presence of intracardiac shunting is discussed in another section of this report.

Intravascular pressures were measured with catheters filled with heparinized saline connected to Bell and Howell pressure transducers (4-327-6223); they were displayed on a patient automated monitor (SG Laboratories, amplifier type SEM 312) with an ultraviolet chart recorder. Mean pulmonary and systemic arterial pressures were measured at each dose level of PG12. Left atrial pressure was measured directly via any atrial septal defect or patent foramen ovale or, in one instance, was taken to be the same as the wedge pressure.

The results were subjected to the following statistical tests. The values of pulmonary blood flow were not normally distributed. The Williams test can only be used on data that is normally distributed, so we analyzed the logarithm of pulmonary blood flow, ln(Qp), which has a normal distribution.35 An overall analysis of variance was performed to compare the effects of the inspired gases (air, 100% oxygen), PG12 level, and any interaction on PAP, PVR, ln(Qp), AoP, heart rate, VO2, and RER. An analysis of variance was also performed with subject and PG12 levels as factors for each inspire separately to compare the effects of the increasing dosage levels with air and 100% oxygen. In both analyses, any missing values (tables 2 and 3) were estimated by the method of least squares. Results after the 5 to 20 ng/kg/min doses of PG12 were compared with those at the basal level (no PG12) for each gas separately by use of the Williams test.36 This test compares each of several increasing dosage levels of a treatment with a control, assuming a stepwise increase or decrease in treatment effect with dose level.

Paired t tests were performed on the pulmonary circulation variables to compare the effect of 100% oxygen and air at the basal level (no PG12), and also to compare the effect of air at the highest dose of 20 ng/kg/min PG12 with 100% oxygen at the basal level. Paired t tests were also used to compare the effects of PG12 at a dose of 20 ng/kg/min on systemic vascular resistance (SVR) and the PVR/SVR ratio.

Results

The results for heart rate and AoP in all 20 patients were analyzed together, but only data from the 16 patients with a PVR above the upper limit of normal for our laboratory (>3 mm Hg · liter-1 · min-1 · m2) formed the basis of the analyses of the pulmonary circulation variables [PAP, ln(Qp), and PVR]. The results of the overall analysis of variance are plotted in figures 1A to 1E. This analysis was used to compare the effects of PG12 when the subjects breathed air with its effects when they breathed 100% oxygen. It was also used to obtain an estimate of the variances for the Williams test.

The results of the Williams test are given in table 2 (air) and table 3 (100% oxygen) and show the lowest dosage level at which a significant increase or decrease in effect occurred. PVR fell with increasing doses of PG12 in patients on air and those on 100% oxygen. This was predominantly due to a rise in pulmonary flow on air and a fall in PAP on 100% oxygen. After PG12 there was evidence of systemic vasodilation: there was a fall in mean AoP and a rise in heart rate in those breathing air and those breathing 100% oxygen.

The results of the paired t tests of the pulmonary circulation variables are given in table 4. When the conditions 100% oxygen, no PG12, and air, no PG12 were compared, the mean PVR was lower and the mean ln(Qp) was higher with 100% oxygen. This was significant at the 1% level. Similar findings have been reported previously.33 When 100% oxygen, no PG12 was compared with air and 20 ng/kg/min PG12, no significant difference was found in PAP, PVR, or ln(Qp). The results of the paired t tests of data on SVR and PVR/SVR ratios are given in table 5. PG12 at a dose of 20 ng/kg/min caused a drop in SVR whether the subjects breathed air or 100% oxygen (p < .05). There was no significant change in PVR/SVR ratio. The 95% confidence limits for the differences are given for those variables for which a significant difference was not found.

We also compared the pulmonary end-capillary blood oxygen content predicted from the alveolar air equation with that measured from a simultaneously drawn sample from the pulmonary vein (table 6). Agreement was good (mean difference = 0.31 ml/100 ml blood, SED = 0.07, 12 samples from 11 subjects).

Ideally, we would have made measurements to confirm that the effects of PG12 did not last longer than 5 min, but the constraints of time prevented this. How-
ever, in five patients we were able to compare baseline measurements before and after the drug run (table 7). PVR values were very similar (mean difference 0.02 U, SED 0.76), confirming the stability of conditions and ventilation during the study and also that the hemodynamic effects of PGI2 are short-lived.

Discussion

We have shown that PGI2 causes dose-dependent pulmonary and systemic vasodilatation in patients with congenital heart disease when infused intravenously at doses of 5 to 20 ng/kg/min. These conclusions rest on some assumptions that we discuss below.

Oxygen consumption was measured by remote respiratory mass spectrometry. This method has been compared with the standard technique using a gas meter and Douglas bag collection. The systematic error in measurement of metabolic gas exchange by remote respiratory mass spectrometry is equal to or less than 0.6% and the standard deviation of single estimates is ± 3%. Oxygen is a selective pulmonary vasodilator, but the difficulty associated with measuring VO2 in subjects breathing pure oxygen has precluded its use in the past. It is important to measure VO2 directly, rather than rely on tables of predicted values. VO2 has been shown to be altered by changes in environmental temperature, the presence of heart malformations, and after cardiac and general surgery. It should also be noted that changes in PAP alone are often insensitive to changes in PVR. Had we only measured PAP, and

FIGURE 1A. This and subsequent figures illustrate results of the overall analysis of variance. This analysis was used to test interactions and for the estimate of comparable treatment means between gases. Significant interactions (p < .05) were noted for ln(Qp) and heart rate only. sed = standard error of difference. Here, a comparison of mean PAP in patients on air and those on oxygen at different levels of PG12 is illustrated.

FIGURE 1B. Comparison of ln(Qp) with air and oxygen at different levels of PG12.
not pulmonary flow, PGI$_2$ would have been discarded as having no pulmonary vasodilator activity. This is in accord with findings of other studies.$^{3,33}$

Blood gas analysis was done on an automatic pH and blood gas electrode system (Corning 165). Studies with blood tonometered with physiologic concentrations of oxygen and carbon dioxide have previously shown that the system measured blood gas tensions to an accuracy of 0.27 kPa. All samples were analyzed within 10 min of collection. The effects of delay have been studied in a previous experiment that showed that the mean fall in oxygen content was 0.15 ml/100 ml after 20 min.$^{33}$

We measured blood gas tensions, and hence blood oxygen contents, rather than measuring blood oxygen contents directly because the instruments available are not particularly suitable for studies in which many blood samples are collected over a short time. The calculation of blood oxygen contents from blood oxygen tension assumes a normal oxygen dissociation curve. It has been shown that prolonged hypoxia may increase the erythrocyte content of 2-3-diphosphogly-
cerate and thus alter the curve. The importance of this has been checked with the use of yeast biotonom-etry in three patients with cyanotic congenital heart disease. They were found to have normal oxhemoglobin dissociation curves. A similar finding has been reported in cyanosed bronchitic patients.

A further assumption of our study was that the RER with 100% oxygen was the same as that with air at the same dose of PGI2. The changes in the ratio within an individual were indeed very small, and analysis of variance showed no significant difference in this ratio or the VO2 at any dosage level of PGI2. This is important, because any change in RER would cause an equal percentage change in cardiac output and resistance. Thus, the effects of PGI2 when added to 100% oxygen are not due to a change in this ratio, and the changes in cardiac output reflect changes in the arteriovenous blood oxygen content differences.

To make a complete set of measurements at each dose level, we would have needed to manipulate the right heart catheter into the pulmonary vein and superi- or and inferior venae cavae, taking samples at each site, and into both atria, measuring the pressures. We thought it was unethical to do this 10 times in the course of the study because of the additional radiation dosage and the extra time required. In our experience, these manipulations perturb the steady state for a few minutes, as shown by a rise in end-tidal PCO2, and so we estimate that these manipulations would have added at least 45 min to the study time. We usually recorded the atrial pressures at least twice during each study, and in no patient did they vary significantly with the dose of PGI2.

In the presence of intracardiac right-to-left shunting, we used the alveolar air equation to predict the oxygen content of pulmonary end-capillary blood, substituting

\[ \text{TABLE 2} \]

Results of the Williams test (subjects breathing air)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dose of PGI2 (ng/kg/min)</th>
<th>SED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>PAP (n = 12)(^a)</td>
<td>52.7</td>
<td>49.1</td>
</tr>
<tr>
<td>PVR (n = 12)(^a)</td>
<td>11.12</td>
<td>9.72(^c)</td>
</tr>
<tr>
<td>ln(Qp) (n = 12)(^a)</td>
<td>1.452</td>
<td>1.610</td>
</tr>
<tr>
<td>AoP (n = 16)</td>
<td>69.8</td>
<td>67.8</td>
</tr>
<tr>
<td>HR (n = 16)</td>
<td>132.9</td>
<td>136.8</td>
</tr>
</tbody>
</table>

\(^a\)One missing value estimated for 20 ng/kg/min.
\(^b\)Significantly different from baseline at 5% level.
\(^c\)Significantly different from baseline at 1% level.
this for pulmonary venous blood in the Fick equation, thus measuring effective pulmonary blood flow. This was necessary in 15 patients. This underestimates total pulmonary blood flow because intrapulmonary right-to-left shunting is not measured. In normal subjects this amounts to less than 5% of total flow.\textsuperscript{46} In 11 patients we assessed the importance of this error by obtaining at least one pulmonary vein sample for comparison. In all cases there was only a small difference between the actual oxygen content in the pulmonary vein sample and the content predicted for pulmonary end-capillary blood (table 6). In three other patients, left ventricular saturation was greater than 98%, despite radiographic evidence of right-to-left shunting at the cardiac level. In one patient, we were unable directly to validate the use of the alveolar air equation to measure the absolute value of pulmonary blood flow. None of our patients had clinical or radiographic evidence of coexistent pulmonary disease, and in all alveolar nitrogen was rapidly washed out in the 100% oxygen environment. Rapid nitrogen washout rules out the presence of large areas of poor ventilation. If there had been important areas of lung that were perfused but poorly ventilated, the alveolar air equation could not have been used in this way. However, even the small discrepancies between pulmonary end-capillary and pulmonary venous blood that we have reported would cause large percentage errors in PVR if arteriovenous oxygen content differences were small. In the absence of alveolar hypoxia, pulmonary end-capillary blood will be nearly fully saturated. If the arteriovenous oxygen content differences are small, pulmonary arterial blood saturation and pulmonary blood flow will be high. In our experience high flows are associated with very low PVRs. In such cases, large percentage changes in PVR result in low absolute changes in measured values that are of no clinical significance. Even the use of pulmonary vein samples may cause inaccuracy under these circumstances, because of the possibility of streaming and regional differences in gas exchange. When pulmonary blood flow

\begin{table}
\centering
\caption{Comparison of PAP, PVR, and (lnQp) with the subjects breathing air alone, breathing air while 20 ng/kg/min PGI\textsubscript{2} was infused, and breathing 100% oxygen alone.}
\begin{tabular}{lcccc}
\hline
 & Mean difference & SED & 95% confidence limits & p value\textsuperscript{a} \\
\hline
Air base vs 100% oxygen & & & & \\
PAP (mm Hg) & 2.2 & 2.6 & -3.4 to 7.8 & \\
PVR (mm Hg·l\textsuperscript{-1}·min\textsuperscript{-1}·m\textsuperscript{2}) & 2.9 & 0.73 & <.01 & \\
(lnQp) (l/min/m\textsuperscript{2}) & -0.365 & 0.092 & <.01 & \\
Air + 20 ng/kg/min PGI\textsubscript{2} vs 100% oxygen & & & & \\
PAP (mm Hg) & 2.7 & 2.5 & -2.8 to 8.3 & \\
PVR (mm Hg·l\textsuperscript{-1}·min\textsuperscript{-1}·m\textsuperscript{2}) & -0.3 & 0.55 & <.01 & \\
(lnQp) (l/min/m\textsuperscript{2}) & 0.142 & 0.112 & <.01 & \\
\hline
\end{tabular}
\textsuperscript{a}Confidence limits are listed for differences that are not significant.
\end{table}

\begin{table}
\centering
\caption{Comparison of baseline measurements of SVR and PVR/SVR (air, 100% oxygen) with values obtained when 20 ng/kg/min PGI\textsubscript{2} was infused (n = 8).}
\begin{tabular}{lcccc}
\hline
 & Baseline on & & & \\
 & air vs air & plus 20 & plus 20 & \\
 & PGI\textsubscript{2} & ng/kg/min & ng/kg/min & \\
\hline
Mean fall in SVR & & & & \\
(mmm Hg·l\textsuperscript{-1}·min\textsuperscript{-1}·m\textsuperscript{2}) & 6.2 & 4.7 & \\
SED & & & & \\
p value & & & & \\
Mean fall in PVR/SVR ratio (%) & & & & \\
SED & & & & \\
95% confidence limits & & & & \\
\hline
\end{tabular}
\end{table}

HR = heart rate.
\textsuperscript{a}n = 15, two missing values estimated for 5 and 15 ng/kg/min, and one missing value estimated for 10 and 20 ng/kg/min.
\textsuperscript{b}n = 17, three missing values estimated for 5 and 15 ng/kg/min, and two missing values estimated for 10 ng/kg/min.
\textsuperscript{c}Significantly different from baseline at 5% level.
\textsuperscript{d}Significantly different from baseline at 1% level.
TABLE 6
Comparison of pulmonary venous blood oxygen content with pulmonary end-capillary blood oxygen content predicted from the alveolar air equation

<table>
<thead>
<tr>
<th>Pulmonary vein saturation</th>
<th>Pulmonary venous blood oxygen content (ml/dl)</th>
<th>Pulmonary end-capillary oxygen content (ml/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100.0(^{a})</td>
<td>20.00</td>
<td>20.38</td>
</tr>
<tr>
<td>99.9(^{a})</td>
<td>19.70</td>
<td>20.39</td>
</tr>
<tr>
<td>96.1</td>
<td>19.46</td>
<td>19.96</td>
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<tr>
<td>99.1(^{a})</td>
<td>20.35</td>
<td>20.42</td>
</tr>
<tr>
<td>98.6</td>
<td>19.83</td>
<td>19.69</td>
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<td>97.1</td>
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<td>99.9(^{a})</td>
<td>24.83</td>
<td>25.21</td>
</tr>
<tr>
<td>98.6</td>
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<td>18.95</td>
</tr>
<tr>
<td>99.9(^{a})</td>
<td>16.46</td>
<td>17.13</td>
</tr>
<tr>
<td>99.9(^{a})</td>
<td>18.22</td>
<td>18.59</td>
</tr>
<tr>
<td>Mean</td>
<td>98.9</td>
<td>19.83</td>
</tr>
<tr>
<td>SD</td>
<td>1.3</td>
<td>2.17</td>
</tr>
</tbody>
</table>

\(^{a}\) Subject breathing 100% oxygen.

is high and arteriovenous oxygen content differences small, it may not be possible to measure flow accurately by the Fick principle.

The use of the alveolar air equation would introduce an error if PGI\(_{2}\) selectively altered flow in intrapulmonary shunts. We found no evidence of this on inspecting the data from four patients in whom there were no intracardiac shunts. In these patients the intrapulmonary shunts could be measured accurately at all doses of PGI\(_{2}\). The numbers are too small for formal statistical testing, but we cannot exclude a selective effect of PGI\(_{2}\) on intrapulmonary shunts in those patients with right-to-left intracardiac shunting, although such an effect has never been reported.

The measurement of systemic flow and hence resistance requires the collection of a sample of mixed venous blood. Blood from the superior and inferior venae cavae has different oxygen contents and, at least in spontaneously breathing adults, respiratory pressure swings may affect flow in each of these vessels to a different extent.\(^{47}\) Thus, a true mixed venous sample can only be obtained after thorough mixing of the two streams, that is beyond the right ventricle. Hence, a true mixed venous sample was unobtainable in most of our patients because of left-to-right shunting, and thus the SVR data presented, based on paired high and low superior vena caval samples, are at best an approximation. They show that at a dose of 20 ng/kg/min, PGI\(_{2}\) caused a fall in SVR with no significant changes in PVR/SVR ratio, suggesting that at least at this dose PGI\(_{1}\) is not a selective pulmonary vasodilator.

Our results show that 100% oxygen and 20 ng/kg/min of PGI\(_{2}\) were equally powerful pulmonary vasodilators. However, when the patients breathed 100% oxygen, the mean AoP rose and remained higher at each dose level compared with the corresponding value when the patients breathed air (figure 1D). Examination of the 95% confidence limits of the measurements suggests that a major difference in efficacy of the two vasodilators with respect to the pulmonary circulation is unlikely. However, oxygen caused a fall in PVR and a rise in AoP, whereas PGI\(_{2}\) caused a fall in both. We also found that oxygen and PGI\(_{2}\) had additive effects on the pulmonary circulation. The analysis of variance confirmed that the effects of PGI\(_{2}\) on PVR were independent of the oxygen tension of the inspirate. It is possible that PGI\(_{2}\) alone in higher doses than we used might have completely reversed any vasoconstriction without the necessity of added oxygen. We were unable to use doses higher than 20 ng/kg/min because of systemic hypotension. It is possible that other infused agents might be able to produce maximal pulmonary vasodilatation without causing severe systemic vasodilation and without the need for additional oxygen.

Due to the nature of the study, all the results of the analyses are confounded with time because neither the order of the dosage levels of treatment nor the choice of gas initially breathed was randomized. We believed that we had to increase the dose of PGI\(_{2}\) slowly because of the risk of hypotension with sudden large doses. Clearly the duration of anesthesia had to be kept as short as possible, so we altered doses as rapidly as we could. Studies in volunteers indicate that the response to PGI\(_{2}\) is fully developed within 3 min, and ends within 5 min of stopping an infusion. If the time to complete response to PGI\(_{2}\) was longer than 5 min we would have underestimated the vasodilator effect in

TABLE 7
Comparison of measurements of PVR before infusion of PGI\(_{2}\) (baseline 1) after stopping the infusion (baseline 2)

<table>
<thead>
<tr>
<th>PVR at baseline 1</th>
<th>PVR at baseline 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>7.5</td>
<td>6.6</td>
</tr>
<tr>
<td>11.0</td>
<td>9.0</td>
</tr>
<tr>
<td>30.3</td>
<td>32.9</td>
</tr>
<tr>
<td>Mean</td>
<td>10.42</td>
</tr>
<tr>
<td>SD</td>
<td>11.81</td>
</tr>
<tr>
<td></td>
<td>12.93</td>
</tr>
</tbody>
</table>
patients breathing air; if the effects of PGI₂ lasted longer than 5 min after stopping the infusion we would have underestimated the additive vasodilator effects of PGI₂ to 100% oxygen. Likewise, if 100% oxygen continued to vasodilate the pulmonary circulation beyond 10 min, we would have underestimated the additive effects of PGI₂. The limited data in table 7 suggest that such an effect is unlikely, at least over the short term. The additional pulmonary vasodilatation already detected, however, is significant. Hence, our conclusions, namely that PGI₂ is at least as powerful a pulmonary vasodilator as 100% oxygen and causes additional pulmonary vasodilation when added to 100% oxygen, remain proven.

Our findings are important in the consideration of the management of children with congenital heart disease. A major factor determining the outcome of corrective surgery is the degree of secondary damage to the pulmonary vascular tree. Elevation of PVR is of two types — fixed irreversible damage, which adversely affects prognosis, and reversible vasoconstriction. It is important to distinguish between the two, or the child may be denied a potentially corrective operation. Traditionally, the assessment of reversible vasoconstriction has been with tolazoline, an α-blocking agent. Tolazoline is not a selective pulmonary vasodilator, and its effects last several hours when given intravenously; both of these features are undesirable in a drug used for preoperative assessment. In addition, tolazoline, when used over the long term, may cause serious side effects including hypotension, gastric hemorrhage, and transient renal failure.

The ideal pulmonary vasodilator would be devoid of effects on the systemic circulation. Unfortunately, PGI₂ does cause systemic hypotension and a fall in SVR, with no definite evidence of a decrease in PVR/SVR ratio. We cannot exclude a selective effect with low doses of PGI₂, but whether the degree of pulmonary vasodilatation so obtained would be useful is questionable. This lack of selectivity may limit its usefulness in this group of patients. Our finding of systemic vasodilatation is similar to the reported effects in normal volunteers and patients with systemic hypertension, ischemic heart disease, and primary pulmonary hypertension.

In conclusion, we have shown that PGI₂ is a powerful pulmonary vasodilator, but its systemic actions necessitate caution in its use. Our findings suggest that oxygen alone, at least in this group of patients, does not unmask all reversible pulmonary vasoconstriction. This may have therapeutic as well as diagnostic implications.

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Circulation. 1986;74:135-144
doi: 10.1161/01.CIR.74.1.135

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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