Prostacyclin-induced Acute Pulmonary Vasodilation in Primary Pulmonary Hypertension

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SUMMARY To evaluate the effects of prostacyclin (prostaglandin I2) on pulmonary vascular tone in primary pulmonary hypertension (PPH), we performed right-heart catheterization on seven patients with PPH and made hemodynamic measurements before and after infusing incremental doses of prostacyclin. In maximal doses of 2–12 ng/kg/min (mean 5.7 ± 3.1 ng/kg/min), prostacyclin reduced mean pulmonary arterial pressure from 62 ± 15 to 55 ± 16 mm Hg (p < 0.05) and total pulmonary resistance from 17.1 ± 8.7 to 9.7 ± 5.9 units (p < 0.005), and increased cardiac output from 4.22 ± 1.64 to 6.57 ± 2.04 l/min (p < 0.01). Heart rate increased from 83 ± 13 to 94 ± 11 beats/min (p = 0.1) and mean systemic arterial pressure decreased from 90 ± 12 to 77 ± 4 mm Hg (p = 0.055). Three patients who received a continuous infusion of prostacyclin for 24–48 hours had sustained reductions in total pulmonary resistance during the infusion period. These data demonstrate that prostacyclin can increase cardiac output and reduce pulmonary arterial pressure and resistance in PPH.

PRIMARY pulmonary hypertension (PPH) is characterized by extreme elevations in pulmonary vascular resistance, which ultimately result in right ventricular failure and death. The cause of this disease is unknown, but prolonged vasoconstriction has been suggested as an etiologic factor. In recent studies demonstrating that vasodilators such as isoproterenol, hydralazine, and diazoxide can reduce pulmonary vascular resistance in PPH provide further evidence that active pulmonary vasoconstriction may be present and potentially reversible in some patients.

Prostacyclin (PGI2), a metabolite of arachidonic acid, is produced in vascular endothelial cells. Intravenous prostacyclin causes pulmonary vasodilation in animals when pulmonary vascular tone is enhanced either by hypoxia or by the infusion of ADP. Prostacyclin reportedly reduced pulmonary vascular resistance in a patient with persistent fetal circulation and in a patient with PPH, and endogenous prostacyclin may be responsible for the reduction in pulmonary vascular tone produced by hydralazine. Since intrapulmonary platelet aggregation, as a result of the reduced pulmonary blood flow, could further compromise the pulmonary circulation in PPH, the potent pulmonary vasodilator and the antiplatelet aggregatory actions of prostacyclin could be beneficial in this disease. We therefore evaluated the hemodynamic effects of i.v. prostacyclin in seven patients with PPH.

Methods

Subjects

Seven patients with PPH entered the study after giving informed consent. All seven patients had symptoms of fatigue and exertional dyspnea, and four had syncopal episodes. The diagnosis of PPH was made after pulmonary function studies, ventilation-perfusion lung scans and cardiac catheterization revealed no evidence of other causes for pulmonary arterial hypertension. Six of the seven patients underwent pulmonary ateriography, which showed no evidence of thromboembolic disease. Echocardiography was performed on all seven patients, and none had abnormal left ventricular dimensions or evidence of valvular disease. Hydrogen or green dye curves were performed on all patients and none showed evidence of an intracardiac shunt. The pulmonary artery wedge pressure was normal in all patients (mean 7 mm Hg, range 4–12 mm Hg). Patient 6 had undergone a portal-systemic shunting procedure in 1968 for gastrointestinal bleeding associated with alcoholic cirrhosis and portal hypertension. In 1977 he was rehospitalized for upper gastrointestinal bleeding, and mesenteric angiography documented closure of the shunt, but he has had no further gastrointestinal symptoms. Two patients were being treated with cardiac glycosides and diuretics, which were continued during the study. The two patients who were taking oral anticoagulants discontinued their use before hospitalization. No patient had received an antiplatelet drug for 2 weeks before the study.

Protocol

Right-heart catheterization was performed using a triple-lumen, balloon-tipped, flotation catheter inserted into a femoral or antecubital vein. A 5% dextrose solution was continuously infused at 20–25 ml/hour through the right atrial port of the catheter to maintain catheter patency and to facilitate the drug administration. A polyethylene catheter was inserted into a femoral, brachial or radial artery for blood sampling and
pressure monitoring. Heart rate was monitored continuously. Mean arterial pressures were obtained by electronic integration of the pressure signals. Baseline cardiac output was measured by the Fick method and by thermodilution (in triplicate) in all patients.

After control hemodynamic measurements were made, a glycine buffer solution (vehicle) was infused at a rate of 1 μl/kg/min using a Harvard infusion pump. Repeat hemodynamic measurements were made 15 minutes later and the glycine buffer solution was exchanged for a prostacyclin solution. Prostacyclin was infused at doses of 2, 4, 8, 10 and 12 ng/kg/min for 15 minutes at each incremental dose, and hemodynamic measurements were made at the end of each dosage period. Cardiac output was measured by thermodilution in all patients during the dose-ranging protocol, which was stopped at a maximal dosage of 12 ng/kg/min or earlier if systemic blood pressure decreased by more than 30%, or if heart rate increased by more than 50% compared with control or if side effects precluded an increase in dosage. Repeat baseline measurements were made no sooner than 30 minutes after the prostacyclin infusion was stopped.

Three patients were maintained on a continuous prostacyclin infusion for 24–48 hours. After the maximal dose was established, the patients were transferred to the cardiac care unit and repeat baseline measurements were made. The prostacyclin infusion was then restarted and gradually increased to the previously established maximal tolerated dose. Hemodynamic measurements were made every 4 hours and after discontinuation of the infusion.

### Results

The maximal hemodynamic effects of prostacyclin are shown in table 1. Mean pulmonary artery pressure decreased in six of the seven patients, and total pulmonary resistance decreased by more than 20% in all patients after prostacyclin. Cardiac output and stroke volume both increased by more than 40%, while heart rate increased slightly. The mean arteriovenous oxygen difference decreased from 7.4 ± 2.0 to 4.4 ± 2.3 ml/dl. The mean systemic arterial pressure fell by more than 5 mm Hg in only three patients.

Figures 1–4 show the hemodynamic effects of incremental doses of prostacyclin. Glycine buffer infusion had no effect compared with control, but prostacyclin decreased total systemic and total pulmonary resistance in a dose-dependent manner. Cardiac output and stroke volume both increased. Despite marked reductions in peripheral vascular resistance, heart rate increased by only 10–20%.

Figure 5 shows the effects of a continuous prostacyclin infusion on total pulmonary resistance in the three patients who were treated for 24–48 hours. Prostacyclin produced a sustained reduction in total pulmonary resistance during the continuous infusion in each patient. Measurements after termination of the infusion were comparable to preinfusion control values.

### Side Effects

The development of side effects with prostacyclin was variable and not completely dose related. Three patients tolerated doses of 8 ng/kg/min or greater for prolonged periods, whereas the other four developed

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### Table 1. Maximal Hemodynamic Effects of Prostacyclin Infusion

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration of symptoms (years)</th>
<th>Dose</th>
<th>SAP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>CO (l/min)</th>
<th>HR (beats/min)</th>
<th>TPR (U)</th>
<th>TSR (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>M</td>
<td>2</td>
<td>Control 8 ng/kg/min</td>
<td>110</td>
<td>40</td>
<td>4.75</td>
<td>96</td>
<td>8.4</td>
<td>23.1</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>F</td>
<td>3</td>
<td>Control 8 ng/kg/min</td>
<td>82</td>
<td>50</td>
<td>4.76</td>
<td>66</td>
<td>10.5</td>
<td>17.2</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>F</td>
<td>3</td>
<td>Control 10 ng/kg/min</td>
<td>78</td>
<td>73</td>
<td>3.20</td>
<td>86</td>
<td>22.8</td>
<td>24.4</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>F</td>
<td>9</td>
<td>Control 4 ng/kg/min</td>
<td>86</td>
<td>56</td>
<td>3.01</td>
<td>98</td>
<td>18.6</td>
<td>28.6</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>F</td>
<td>2</td>
<td>Control 2 ng/kg/min</td>
<td>88</td>
<td>82</td>
<td>2.63</td>
<td>91</td>
<td>31.2</td>
<td>33.5</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>M</td>
<td>10</td>
<td>Control 2 ng/kg/min</td>
<td>83</td>
<td>58</td>
<td>7.43</td>
<td>72</td>
<td>7.8</td>
<td>11.2</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>F</td>
<td>2</td>
<td>Control 6 ng/kg/min</td>
<td>101</td>
<td>76</td>
<td>3.73</td>
<td>75</td>
<td>20.4</td>
<td>27.1</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>90</td>
<td>62</td>
<td>4.22</td>
<td>83</td>
<td>17.1</td>
<td>23.6</td>
</tr>
</tbody>
</table>

| PG12 (5.7 ± 3.1 ng/kg/min) | 77 | 55 | 6.57 | 94 | 9.7 | 13.1 |
| Mean ± SD | 7 ± 4 | ±16 | ±2.04 | ±11 | ±5.9 | ±5.4 |

*p* = 0.055 < 0.05 < 0.01 0.1 < 0.005 < 0.001

Abbreviations: SAP = mean systemic artery pressure; PAP = mean pulmonary artery pressure; CO = cardiac output; HR = heart rate; TPR = total pulmonary resistance; TSR = total systemic resistance.
side effects at lower doses, which prevented further dose-ranging studies or a continuous infusion. Headache occurred in six patients, and was mild in three. Four patients had nausea and two had vomiting. Cutaneous flushing was observed in five patients. Patient 4, who had a history of head trauma and pseudotumor cerebri for which a craniotomy was performed in 1967, developed diplopia at 6 ng/kg/min, which subsided 30 minutes after the discontinuation of the infusion. Patients 4 and 6 had systemic hypotension during the dose-ranging segment, but blood pressure returned to preinfusion levels within 5 minutes after the prostacyclin infusion was stopped. Patient 1 had a significant reduction in systemic blood pressure during continuous infusion, but no symptoms developed and the infusion was continued without complication.

**Discussion**

The renewed interest in disorders of the pulmonary circulation has led to the demonstration that several systemic vasodilators may reduce pulmonary vascular tone. Our study shows that prostacyclin, one of the most potent pulmonary vasodilators, markedly reduced pulmonary vascular resistance in a dose-dependent manner in all seven patients studied; this hemodynamic effect was sustained in several patients during a 24–48-hour continuous infusion. These observations demonstrate that even in patients with severe, chronic
pulmonary hypertension, there is a component of active pulmonary vasoconstriction that responds to a potent pulmonary vasodilator.

The clinical diagnosis of PPH in our patients was based on the presence of severe precapillary pulmonary hypertension in the absence of demonstrable valvular heart disease, pulmonary thromboembolism, intracardiac shunting, or significant parenchymal lung disease. We have no data on left ventricular volumes or ejection fraction, so we cannot exclude the presence of coexistent left ventricular dysfunction. It is unlikely that left ventricular dysfunction contributed to the presence of pulmonary hypertension in our patients, since all had a normal pulmonary artery wedge pressure at catheterization and a normal left ventricular chamber size by echocardiography.

A major concern about instituting vasodilator therapy for PPH is the risk of producing severe systemic hypotension if the drug reduces systemic vascular resistance without affecting pulmonary vascular tone. The risk is compounded by the fact that all of the vasodilators reported to be useful in reducing pulmonary vascular tone are neither highly selective nor preferential for the pulmonary arterial bed, by the difficulty in titrating the dose of a vasodilator to the optimal hemodynamic effect, and by the prolonged duration of effect of several of the currently used vasodilators. Rubino and Schroeder reported a patient who manifested no change in systemic blood pressure with incremental doses of i.v. diazoxide up to 180 mg, but developed refractory hypotension and died after she was given a bolus of 300 mg. The ability to titrate the dose of prostacyclin to the desired hemodynamic effect, its potency as a pulmonary vasodilator, and the ability to reverse rapidly any adverse effect by discontinuing the infusion make prostacyclin a safe agent for initial testing of a patient's responsiveness to vasodilators.

Three patients tolerated a continuous infusion of prostacyclin at doses of 8–10 ng/kg/min, with complaints of only mild nausea or headache, whereas at lower doses, the four other patients developed more severe symptoms that precluded further use of the drug. Data et al. recently reported that healthy volunteers could tolerate infusions of prostacyclin at doses up to 10 ng/kg/min for as long as 60 minutes, although most subjects had side effects at doses above 4 ng/kg/min. No subject in that study could tolerate an infusion of 4 ng/kg/min for 24 hours. Three of our patients were maintained on a continuous infusion at 8 or 12 ng/kg/min for 24 hours; compared with normals, patients with PPH may either be more resistant to the vascular effects of prostacyclin or they may metabolize prostacyclin differently.

In conclusion, prostacyclin reduced pulmonary vascular resistance in a dose-dependent manner in seven patients with severe PPH. The hemodynamic effects persisted during a continuous 24–48-hour infusion in three patients. Side effects, including systemic hypotension in two patients, were reversed rapidly by reducing the dosage or by stopping the infusion. Prostacyclin may be a useful drug in the initial evaluation of vasodilator therapy and in the short-term management of seriously ill patients with PPH.

Acknowledgments

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Prevention of Lipid Accumulation in Experimental Vein Bypass Grafts by Antiplatelet Therapy

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SUMMARY The ameliorative effect of antiplatelet therapy on atherogenesis of vein grafts was assessed in autologous cephalic veins grafted into femoral arteries of 16 normolipemic and 11 hyperlipemic stump-tailed macaque monkeys. Before grafting, one half of each vein was distended at high pressure (700 mm Hg) and the other half at low pressure (350 mm Hg). Eight normolipemic monkeys were treated with aspirin, 80 mg/day, and dipyridamole, 50 mg/day, and eight were controls. When grafts were harvested at 12 weeks, tissue cholesterol and β-aminoprotein content in grafts from untreated monkeys were significantly higher than in ungrafted, uninjured veins. Antiplatelet therapy eliminated the increase in lipid content of vein segments distended at low pressure, and significantly lowered lipid content of segments distended at high pressure, though not to the control levels of ungrafted veins. Seven of the 11 hyperlipemic monkeys received antiplatelet drugs and four did not. The lipid content of all graft segments was significantly higher than in grafted or ungrafted veins from normolipemic monkeys. Antiplatelet therapy again significantly reduced the lipid content in vein segments distended at both levels of pressure, and also reduced the elevated cholesterol content in ungrafted veins. Although this animal preparation differs in many ways from human coronary bypass operations, these observations may be pertinent to the prevention of atherosclerosis in human vein bypass grafts.

SAPHENOUS VEIN aortocoronary bypass grafts can develop atherosclerotic changes that lead to graft stenosis or occlusion.1,2 The pathogenesis of these atherosclerotic changes in vein grafts is probably similar to that of atheroma in native arteries, although the process is accelerated. According to the most prevalent hypotheses about atherogenesis,3 endothelial injury exposes the subendothelial connective tissue to platelets and other blood constituents. Platelets adhere to the subendothelial collagen, aggregate, and release the contents of their granules. The massive infiltration of platelet contents, plasma lipoproteins, and possibly other blood components leads to focal proliferation of smooth muscle cells in the vessel wall stimulated by a mitogenic factor released by platelets, to formation of connective tissue matrix, and to deposition of lipids.

Since some degree of trauma to vein grafts during harvesting and preparation for coronary revasculariza-
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