Treatment of primary pulmonary hypertension with intravenous epoprostenol (prostacyclin)

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SUMMARY Ten patients with severe primary pulmonary hypertension and pronounced disability who were unresponsive to oral vasodilators were treated with intravenous epoprostenol (prostacyclin). All had been referred for heart and lung transplantation. Short term administration of epoprostenol (mean dose 5.5 ng/kg/min) increased the mean cardiac index from 1.8 to 2.2 l/min/m², improved pulmonary artery oxygen saturation from 48% to 57%, and increased calculated tissue oxygen delivery from 10 to 11.8 ml/kg/min. The mean pulmonary vascular resistance fell by 18% while mean systemic artery pressure fell by 32%. Pulmonary artery pressure rose in only two patients. Continued intravenous infusion of epoprostenol for 1–25 months was associated with subjective and clinical improvement. Exercise tolerance improved as measured by an increase in the maximum rate of oxygen consumption during progressive exercise testing. In those six patients who were able to exercise before treatment it rose from a mean of 7 to 15 ml/kg/min. Those who had been unable to exercise before treatment achieved comparable rates of oxygen consumption after treatment. Two patients died on treatment, three have undergone heart-lung transplantation, and in five the treatment is continuing. Complications included episodes of sepsicaemia and ascites.

In this uncontrolled study of patients with severe pulmonary hypertension epoprostenol seemed to offer a means of optimally dosing the patients with a vasodilator to reduce pulmonary vascular resistance and thus increasing cardiac output and oxygen tissue delivery. There was no evidence to suggest that this treatment influenced the progress of the disease.

Primary pulmonary hypertension is defined as pulmonary arterial hypertension of unknown cause,¹ and has been shown to be associated with three distinct pulmonary diseases²: pulmonary veno-occlusive disease, which can have characteristic clinical features,³ so called recurrent thromboembolism; and plexogenic arteriopathy. Most clinicians regard plexogenic pulmonary arteriopathy as true primary pulmonary hypertension but it can be difficult to distinguish this disease from thrombotic pulmonary hypertension on the basis of clinical or haemodynamic variables.⁴ Primary pulmonary hypertension has a poor prognosis and no treatment has been shown to reverse its progress.⁵

Oral vasodilator treatment can reduce the increased pulmonary vascular resistance and increase the low cardiac output characteristic of the disease,⁶ ⁷ and sustained clinical improvement has been reported in a small proportion of patients. Such treatment can also produce severe and refractory systemic hypertension.⁸ ⁹

An intravenous infusion of epoprostenol (prostacyclin) induced short term pulmonary vasodilatation in primary pulmonary hypertension.¹⁰ Because of its short half life, the dose can be titrated to produce a desired haemodynamic effect and any adverse effects are reversed immediately by discontinuing the infusion. It is a safe agent to use for the initial testing of a patient’s responsiveness to a vasodilator¹⁰ but it has not been used on a long term basis because no oral preparation is available. We have previously shown that long term treatment of primary pulmonary hypertension can be achieved.

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with intravenous epoprostenol and we now report on the successes, problems, and failures of this treatment in ten patients, including our original patient.

Patients and methods

Patients

Ten patients diagnosed as having primary pulmonary hypertension were seen at our unit between November 1982 and January 1985. The six women and four men (mean age 30 years) had had symptoms for an average of 30 months and the mean time since diagnosis was 6 months. All were severely disabled by breathlessness and fatigue. Table 1 shows details of the individual patients. Five patients had suffered syncopal episodes, two had angina on minimal exertion, and all but patients 5 and 7 had clinical signs of right ventricular failure. The diagnosis of primary pulmonary hypertension had been reached in each patient after the exclusion of other causes of pulmonary hypertension by chest radiography, pulmonary function testing, echocardiography, isotope ventilation-perfusion imaging, and cardiac catheterisation. All except patients 4 and 8 had undergone pulmonary angiography and in each case this had been reported as showing no evidence of major vessel thromboembolism. Patient 8 had normal ventilation perfusion lung scans. In six patients histological material was examined. Patients 4, 5, and 10 underwent open lung biopsy, and later patients 1, 3, and 5 had both lungs removed during heart-lung transplantation. A necropsy was performed on patient 2.

All patients but one were receiving oral anticoagulants, six were taking diuretics, four were taking digoxin, and four required oxygen. All patients had received a trial of treatment with at least one vasodilator. The methods for assessing response had varied (table 2) but no patient had reported subjective improvement while taking oral vasodilators.

All patients were referred to our unit to be considered for heart-lung transplantation because of their poor clinical condition, which had worsened despite treatment. Table 3 shows data collected by their referring physicians 1–18 (mean 5·5) months before catheterisation at our unit. Not all the measured

Table 1 Data on 10 patients with primary pulmonary hypertension

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Duration of symptoms (months)</th>
<th>Time since diagnosis (months)</th>
<th>Clinical severity of disability</th>
<th>Drug treatment</th>
<th>Biopsy specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>28</td>
<td>78</td>
<td>8</td>
<td>Confined to hospital ward</td>
<td>Spironolactone, Frusemide, Continuous oxygen, Warfarin</td>
<td>100 mg daily, 160 mg daily</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>38</td>
<td>16</td>
<td>12</td>
<td>Confined to hospital ward</td>
<td>Digoxin, Spironolactone, Frusemide, Bendroflauzide, Oxygen, Warfarin</td>
<td>100 mg daily, 80 mg daily, 5 mg daily, 18 h/day</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>21</td>
<td>14</td>
<td>10</td>
<td>Unable to walk 300 m</td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>38</td>
<td>60</td>
<td>4</td>
<td>Unable to walk 200 m</td>
<td>Bumetanide, Oxygen at night, Warfarin</td>
<td>2 mg daily</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>39</td>
<td>12</td>
<td>2</td>
<td>Unable to climb one flight of stairs</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>24</td>
<td>16</td>
<td>1-5</td>
<td>Unable to walk 100 m</td>
<td>Digoxin, Warfarin, Cyclopentiazide</td>
<td>0.1 mg daily</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>17</td>
<td>23</td>
<td>3</td>
<td>Confined to a wheelchair</td>
<td>Digoxin, Disopyramide, Warfarin</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>32</td>
<td>48</td>
<td>40</td>
<td>Confined to a wheelchair</td>
<td>Oxygen, Digoxin, Frusemide, Warfarin</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>34</td>
<td>5</td>
<td>1</td>
<td>Unable to walk 300 m</td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>32</td>
<td>31</td>
<td>27</td>
<td>Unable to walk 50 m</td>
<td>Frusemide, Amiloride, Warfarin</td>
<td>80 mg daily, 10 mg daily</td>
</tr>
</tbody>
</table>

NA, not available.
variables were determined in every patient, but the available data showed a deterioration in their pulmonary vascular resistance (PVR) and pulmonary arterial oxygen saturation (Pao₂ saturation) and a significant rise in the mean pulmonary arterial pressure (PAP). This supports the clinical observation that the patients' conditions were rapidly deteriorating.

**HAEMODYNAMIC MEASUREMENTS**

The effect of short term administration of epoprostenol was assessed in each patient after we stopped anticoagulant treatment and obtained written informed consent. A triple lumen flow directed catheter was used to perform right heart catheterisation in a supine patient. Mean right atrial, pulmonary arterial, and pulmonary arterial wedge pressures (RAP, PAP, and PAWP) were obtained by electronic integration of the pressure signals with the midaxillary line as the zero reference level. Mean systemic arterial pressure (SAP) and heart rate (HR) were monitored continuously via a radial artery cannula and electrocardiograph. Radial arterial oxygen saturation and pulmonary arterial oxygen saturation were determined by a blood gas analyser (ABL 3 Radiometer, Copenhagen, Denmark) and cardiac output (CO) by thermocatheter and a bedside cardiac output computer (American Edwards Laboratories, Santa Ana, California, USA). The following formulas were used to calculate further indices.

Cardiac index (CI) = \( \frac{CO}{SBP} \) mmHg

Pulmonary vascular resistance (PVR) = \( \frac{\text{mean PAP} - \text{mean PAWP}}{\text{CO}} \times 80 \) dyn cm⁻² s⁻¹

Systemic vascular resistance (SVR) = \( \frac{\text{mean SAP} - \text{mean RAP}}{\text{CO}} \times 80 \) dyn cm⁻² s⁻¹

\( O_2 \) content = \( \frac{O_2 \text{ saturation} \times O_2 \text{ capacity}}{100} + \text{dissolved } O_2 \)

where \( O_2 \) capacity = Hb (g/dl) \times 1.36

Peripheral \( O_2 \) delivery = arterial \( O_2 \) content \times CO (ml/min)

Epoprostenol (Flolan) was supplied by Wellcome Foundation Ltd (Beckenham, Kent) as the sodium salt and made up for infusion in a sterile glycine buffer. After baseline measurements had been obtained it was administered as an initial infusion of 2 ng/kg/min through a peripheral vein. The dosage

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**Table 2** Details of previous vasodilator treatment and its effect

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drug</th>
<th>Daily dose (mg)</th>
<th>Route</th>
<th>Duration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydralazine</td>
<td>50</td>
<td>Oral</td>
<td>2 days</td>
<td>Stopped due to syncope</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>60</td>
<td>Oral</td>
<td>6 weeks</td>
<td>No subjective improvement</td>
</tr>
<tr>
<td></td>
<td>Isosorbide</td>
<td>20</td>
<td>Oral</td>
<td>6 weeks</td>
<td>No subjective improvement</td>
</tr>
<tr>
<td>2</td>
<td>Nifedipine</td>
<td>10</td>
<td>Oral</td>
<td>1 dose</td>
<td>No reduction in PVR</td>
</tr>
<tr>
<td></td>
<td>Diazoxide</td>
<td>300</td>
<td>Into PA</td>
<td>1 dose</td>
<td>No reduction in PVR</td>
</tr>
<tr>
<td>3</td>
<td>Hydralazine</td>
<td>50</td>
<td>Oral</td>
<td>1 day</td>
<td>Stopped due to nausea</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>30</td>
<td>Oral</td>
<td>4 weeks</td>
<td>No subjective improvement</td>
</tr>
<tr>
<td>4</td>
<td>Glyceril trinitrate</td>
<td>0-5</td>
<td>Sublingual</td>
<td>1 day</td>
<td>Reduced PVR by 37%</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>10</td>
<td>Oral</td>
<td>1 dose</td>
<td>Reduced PVR by 12%</td>
</tr>
<tr>
<td></td>
<td>Diazoxide</td>
<td>60</td>
<td>Oral</td>
<td>4 weeks</td>
<td>No subjective improvement</td>
</tr>
<tr>
<td>5</td>
<td>Hydralazine</td>
<td>400</td>
<td>Oral</td>
<td>4 weeks</td>
<td>No increase in exercise tolerance</td>
</tr>
</tbody>
</table>

PA, pulmonary artery; PVR, pulmonary vascular resistance.

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**Table 3** Haemodynamic data (mean (SEM)) at previous catheterisation compared with measurements at our unit. (Figures in parentheses are the numbers of patients in which the individual measurements were compared.)

<table>
<thead>
<tr>
<th></th>
<th>Previous catheterisation</th>
<th>Our catheterisation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAP (10) (mm Hg)</td>
<td>66 (6)</td>
<td>76 (6)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>PVR (6) (dyn s cm⁻²)</td>
<td>1354 (200)</td>
<td>1634 (225)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Pao₂ (5) saturation (%)</td>
<td>62 (2)</td>
<td>49 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI (5) (l/min/m²)</td>
<td>2.2 (0.2)</td>
<td>1.8 (0.2)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; Pao₂, pulmonary arterial oxygen saturation; CI, cardiac index.
was increased by 1 ng/kg/min every 15 minutes and the haemodynamic measurements were repeated before each dose increment. The protocol was continued until a significant (20%) change in pulmonary vascular resistance or systemic arterial pressure was observed or side effects occurred.

**LONG TERM TREATMENT**

After the short term trial the patients were started on long term intravenous treatment. A cannula (149 Nutricath no 218.20, Vygon UK Ltd, Cirencester) was inserted through a subcutaneous tunnel into a subclavian vein and connected via a length of sterile manometer tubing and a three way stopcock to a 20 ml syringe containing the infusion. This was protected from light and administered continuously by a battery driven syringe pump with an automatic auditory alarm (MS16A, Graseby Dynamics, Bushey, Hertfordshire). The pump was carried in a small shoulder holster and the infusion system did not restrict the patients’ mobility. The patients were taught how to prepare, store, administer, and maintain the infusion themselves so that they could live independently at home.

**ASSESSMENT OF RESPONSE TO TREATMENT**

The long term infusion was started at the maximal dose that had been comfortably tolerated during the short term trial. The patients’ subjective feelings of well-being and their exercise tolerance were assessed during treatment. Clinical signs and the need for concomitant drug treatment were regularly reviewed. Patients had formal exercise testing before the start of epoprostenol treatment, if they were well enough, and at convenient intervals after start of the long term infusion. This consisted of walking on the level on a heavy duty electrically driven treadmill. The speed was increased by 0·9 km/h every minute until the patient felt unable to continue. At rest and then during the test oxygen consumption was calculated for each minute by measuring the partial pressure of mixed expired oxygen with a mass spectrometer and the total volume expired was measured with a pneumotachograph. The maximum walking speed (WS) attained in km/h and the maximum oxygen consumption attained in ml/kg/min (V Max O2) were recorded.

In an attempt to obtain maximum clinical benefit seven of the patients had one or more dosage increments during their long term treatment. Each increase was achieved during a period of hospital admission in which the systemic blood pressure was closely monitored.

The paired t test was used for statistical analysis of recorded data before and after intervention.

**Results**

**SHORT TERM EFFECTS OF EPOPROSTENOL**

The baseline measurements confirmed the presence of severe pulmonary hypertension in the 10 patients. Mean pulmonary artery pressure and pulmonary

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**Table 4 Values for haemodynamic data at baseline and during maximal dose infusion during short term epoprostenol trial**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Max dose of epoprostenol</th>
<th>SAP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>PVR (dyn s cm⁻¹)</th>
<th>SVR (dyn s cm⁻¹)</th>
<th>HR (beats/min)</th>
<th>Pao₂ saturation</th>
<th>O₂ delivery (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Baseline</td>
<td>78</td>
<td>100</td>
<td>1·7</td>
<td>2133</td>
<td>1600</td>
<td>104</td>
<td>45</td>
<td>5-8</td>
<td></td>
</tr>
<tr>
<td>2 Baseline</td>
<td>82</td>
<td>71</td>
<td>1·5</td>
<td>1899</td>
<td>1992</td>
<td>70</td>
<td>38</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>3 Baseline</td>
<td>66</td>
<td>68</td>
<td>1·9</td>
<td>1365</td>
<td>1223</td>
<td>82</td>
<td>45</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>4 Baseline</td>
<td>80</td>
<td>55</td>
<td>1·7</td>
<td>1376</td>
<td>1952</td>
<td>98</td>
<td>52</td>
<td>10-9</td>
<td></td>
</tr>
<tr>
<td>5 Baseline</td>
<td>65</td>
<td>65</td>
<td>1·8</td>
<td>1629</td>
<td>1425</td>
<td>104</td>
<td>53</td>
<td>11-9</td>
<td></td>
</tr>
<tr>
<td>6 Baseline</td>
<td>83</td>
<td>80</td>
<td>2·1</td>
<td>1558</td>
<td>1684</td>
<td>87</td>
<td>60</td>
<td>9-5</td>
<td></td>
</tr>
<tr>
<td>7 Baseline</td>
<td>75</td>
<td>80</td>
<td>2·6</td>
<td>1242</td>
<td>1174</td>
<td>90</td>
<td>70</td>
<td>11-6</td>
<td></td>
</tr>
<tr>
<td>8 Baseline</td>
<td>73</td>
<td>62</td>
<td>3-0</td>
<td>784</td>
<td>1094</td>
<td>90</td>
<td>51</td>
<td>15-2</td>
<td></td>
</tr>
<tr>
<td>9 Baseline</td>
<td>72</td>
<td>48</td>
<td>3-1</td>
<td>580</td>
<td>1020</td>
<td>90</td>
<td>61</td>
<td>16-8</td>
<td></td>
</tr>
<tr>
<td>10 Baseline</td>
<td>93</td>
<td>60</td>
<td>1·5</td>
<td>1583</td>
<td>2187</td>
<td>77</td>
<td>42</td>
<td>8-5</td>
<td></td>
</tr>
<tr>
<td>11 Baseline</td>
<td>80</td>
<td>60</td>
<td>1·8</td>
<td>1358</td>
<td>1457</td>
<td>84</td>
<td>56</td>
<td>9-5</td>
<td></td>
</tr>
<tr>
<td>12 Baseline</td>
<td>100</td>
<td>80</td>
<td>1·8</td>
<td>1800</td>
<td>2275</td>
<td>78</td>
<td>51</td>
<td>12-4</td>
<td></td>
</tr>
<tr>
<td>13 Baseline</td>
<td>80</td>
<td>80</td>
<td>2·1</td>
<td>1516</td>
<td>1579</td>
<td>82</td>
<td>57</td>
<td>14-3</td>
<td></td>
</tr>
<tr>
<td>14 Baseline</td>
<td>70</td>
<td>50</td>
<td>2·2</td>
<td>869</td>
<td>1440</td>
<td>63</td>
<td>60</td>
<td>11-8</td>
<td></td>
</tr>
<tr>
<td>15 Baseline</td>
<td>61</td>
<td>48</td>
<td>2·8</td>
<td>675</td>
<td>1031</td>
<td>68</td>
<td>68</td>
<td>15-1</td>
<td></td>
</tr>
<tr>
<td>16 Baseline</td>
<td>95</td>
<td>105</td>
<td>1·5</td>
<td>2744</td>
<td>2425</td>
<td>84</td>
<td>43</td>
<td>8-3</td>
<td></td>
</tr>
<tr>
<td>17 Baseline</td>
<td>70</td>
<td>105</td>
<td>2·0</td>
<td>2054</td>
<td>1340</td>
<td>96</td>
<td>57</td>
<td>10-9</td>
<td></td>
</tr>
<tr>
<td>Mean (SEM) Baseline</td>
<td>85 (3)</td>
<td>76 (6)</td>
<td>1·83 (0·2)</td>
<td>1727 (202)</td>
<td>1837 (129)</td>
<td>83 (4)</td>
<td>48 (2)</td>
<td>10-0 (1)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0·001</td>
<td>&gt;0·4</td>
<td>&lt;0·005</td>
<td>&lt;0·02</td>
<td>&lt;0·001</td>
<td>&lt;0·005</td>
<td>&lt;0·001</td>
<td>&lt;0·001</td>
<td></td>
</tr>
</tbody>
</table>

SAP, systemic arterial pressure; PAP, pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; HR, heart rate; Pao₂ sat, pulmonary arterial oxygen saturation; O₂ delivery, peripheral oxygen delivery.
vascular resistance were high and cardiac index and pulmonary arterial oxygen saturation were low (table 4). There was a significant fall in pulmonary vascular resistance after epoprostenol. This was small and of doubtful physiological significance in four and large in three. There was a statistically significant decrease in the mean systemic arterial pressure and systemic vascular resistance and a statistically significant rise in the mean cardiac index. Mean pulmonary arterial oxygen saturation rose from 48% to 57% and the mean peripheral oxygen delivery from 10 to 11.8 ml/kg/min. There was a

Fig 1  Individual exercise tolerances expressed as maximum oxygen consumption at various times before and after starting epoprostenol. ↑ Epoprostenol started.
small increase in mean heart rate during the infusion but no change in pulmonary arterial wedge or right atrial pressures. The mean falls in pulmonary vascular and systemic vascular resistances were 19% and 32% respectively. In only two patients (1 and 5) was the fall in pulmonary vascular resistance greater than the fall in systemic vascular resistance.

**EFFECTS OF LONG TERM EPOPROSTENOL**

All but patient 9 noted a subjective improvement in well-being and exercise tolerance within a week of starting long term treatment. The subjective benefit was confirmed on formal exercise testing (fig 1). Four patients were too ill to exercise before epoprostenol but after long term treatment they reached a mean walking speed (SEM) of 4 (0.6) km/h and a mean maximum oxygen consumption of 13.4 (2.0) ml/kg/min. The six patients who exercised shortly before starting epoprostenol increased their mean walking speed from 2.5 (0.7) to 4.3 (0.6) km/h (p < 0.01) and their maximum oxygen consumption from 7.2 (0.7) to 14.9 (1.4) ml/kg/min (p < 0.01). All patients showed an initial improvement in exercise performance during epoprostenol treatment. Figure 1 shows that individual exercise performances continued to improve or were sustained in some patients while in others improvement was only temporary. Subjective benefit was held to be present if the patients reported improved symptoms and exercise tolerance that worsened within 30 minutes of the infusion being interrupted.

**CLINICAL PROGRESS**

Figure 2 shows that five patients have felt better on epoprostenol for over 24 weeks to 2 years.

All patients (except patient 6) initially were able to leave hospital and return home to an improved quality of life. Three of the patients have since undergone heart-lung transplantation. Patients 1 and 3 remained well on the infusion until short periods of deterioration prompted operation. Patient 5 did well initially but then suffered two episodes of sepsicaemia, the second of which was associated with a cardiorespiratory arrest. She slowly recovered and subsequently had a heart-lung transplant.

After initial improvement patient 6 had a relapse into refractory right ventricular failure after a cardiorespiratory arrest during follow up cardiac catheterisation. This event was not associated with any change in epoprostenol dosage and appeared to occur during repositioning of the catheter. Recurrent massive ascites and renal failure developed and the patient died five months after starting treatment. After an impressive initial response, patient 2 slipped back to her previous condition. The infusion was stopped for a short time and reintroduction of epoprostenol at a higher dose was associated with a further impressive response. After 10 months' treatment, however, she relapsed into gross right ventricular failure which was unresponsive to an increasing dose of epoprostenol.

The other five patients have received epoprostenol for a comparatively short time but all report sustained benefit.

**SIDE EFFECTS OF LONG TERM TREATMENT**

In three patients sepsicaemia developed from infection at the tip of the indwelling cannula. In each case this was associated with a deterioration in well-being and exercise ability. In patients 1 and 3 it responded...
quickly to intravenous antibiotics and replacement of the intravenous cannula. In patient 5 two courses of antibiotics and resiting of the subclavian cannula did not eradicate the infection. Epoprostenol had to be given through a peripheral vein until the infection was controlled; then a further subclavian line was inserted.

Sterile ascites developed in three patients during long term treatment. In each case the fluid was straw coloured and contained a predominance of lymphocytes. The glucose and amylase concentrations of the fluid were normal but in each case the total protein content was > 35 g/l and electrophoresis showed a protein leak which was non-selective according to the results of molecular weight determinations. No patient had a raised erythrocyte sedimentation rate at diagnosis and in two of the patients tested antinuclear factor, DNA binding, and rheumatoid factor were not detected in the peripheral blood. Liver function tests showed a slight increase in aspartate aminotransferase concentrations. Patient 1 had normal computed tomographs of the liver and abdomen.

In patient 1 the ascites did not recur after paracentesis. In patient 2 it became massive and required repeated aspiration. In patient 6 it was massive, recurrent, and became chylous shortly before death. In all three patients the ascites was greater than would be expected from right ventricular failure alone and was not associated with generalised fluid retention of the same magnitude.

Higher doses of epoprostenol were tolerated by the patients than by normal volunteers. This was achieved without the commonly reported side effects of headache, flushing, and abdominal pain. When these side effects did occur they were associated with an increase in the infusion dose but they were transient in nature, and normally subsided within 24 hours. We learnt to control side effects by increasing the infusion rate more gradually. In general the patients managed their treatment with very few problems. Five patients experienced sudden interruptions in their infusions; one because of pump failure, one because the line became disconnected, and three because they inadvertently turned off the pump. All noticed a considerable increase in symptoms within minutes and a prompt improvement when the infusion was restarted.

PATHOLOGICAL EXAMINATION
Histological specimens obtained in six patients showed medial hypertrophy of the pulmonary arteries with widespread fibrocellular proliferation of the intima of all arteries and arterioles. In patients 1, 4, and 5 the changes were typical of plexiform pulmonary arteriopathy but in patients 2, 3, and 10 the vascular changes were associated with the presence of thrombi in peripheral pulmonary arteries. Patient 5 had an open lung biopsy before epoprostenol and both lungs were available for examination after heart-lung transplantation. There was no difference in the severity of the vascular lesions between the two specimens.

Discussion
This paper is not the report of a clinical trial but rather the observations of the effect of a treatment on ten patients with a severe, potentially fatal condition. Nevertheless, we made several important observations based on the subjective and objective data. These patients were treated with epoprostenol because all had severe primary pulmonary hypertension with a high pulmonary artery pressure and pulmonary vascular resistance and low cardiac index. All had a pulmonary arterial oxygen saturation below 63%, which is associated with a three year survival rate of < 20%. In all, the symptoms were becoming worse and this was confirmed by haemodynamic measurements, a fall in pulmonary arterial oxygen saturation between catheterisations, and in four a measured decline in exercise capacity and maximum oxygen consumption. None had responded to conventional oral vasodilators.

The rationale behind the use of vasodilators in primary pulmonary hypertension is that the histological features of the condition may represent an inappropriate constriction of the pulmonary vasculature. In the early stages of the disease the vasoconstriction is labile and responsive to vasodilators but later it becomes fixed and irreversible. Short term administration of vasodilators in primary pulmonary hypertension most commonly causes a decrease in the pulmonary and systemic vascular resistance and an associated increase in cardiac output with little or no effect on the pulmonary artery pressure. These haemodynamic changes can be sustained with long term oral treatment and can be associated with clinical and subjective improvement in the patient’s condition. The administration of vasodilators with long half lives can also cause profound systemic hypotension that is resistant to treatment and can lead to death. Epoprostenol is a powerful vasodilator when it is administered intravenously. It has a rapid onset of action that is dose dependent. It has a short half life so any adverse reaction can be rapidly reversed by discontinuing the infusion. The optimal dose of the infusion can be determined during a single right heart catheterisation. Most studies can be completed in two hours which is a much shorter time than that required for fully testing orally administered drugs. When epoprostenol is administered as a long term
infusion, fluctuations in the blood concentration due to variable bioavailability are avoided, thus making it ideally suited to treatment of critically ill patients. It is possible that the problem with oral vasodilators is the maintenance of adequate concentrations in the blood.

The effect of short term infusion of epoprostenol in our patients was similar to that reported previously. Some workers have claimed that in order to establish a pulmonary vasodilation effect, there should be a fall in pulmonary artery pressure and the pulmonary vascular resistance should decrease more than systemic vascular resistance. Only two of our patients fulfilled these criteria. The cardiac output, however, improved with no rise in pulmonary artery pressure in all but two patients. This improved cardiac output was associated with concomitant increases in pulmonary arterial oxygen saturation and peripheral oxygen delivery. The increase in cardiac output was achieved without a large increase in heart rate or a change in right atrial pressure, suggesting there was no important increase in right ventricular workload.

In assessing the effect of long term epoprostenol, the ideal would be to repeat haemodynamic measurements. Right heart catheterisation is not without complications, however, and in primary pulmonary hypertension is associated with a significant morbidity and mortality as we witnessed in patient 6. Also although our patients' recordings were stable during their catheterisations, there can be spontaneous variability of haemodynamic function in primary pulmonary hypertension. Because the increase in cardiac output was the major effect of epoprostenol we monitored our patients' progress non-invasively by means of treadmill exercise testing. Measurement of symptom limited maximum oxygen consumption has been shown to correlate with the cardiac output in normal subjects and patients with left heart failure. A recent paper has recommended its use also in assessing the response to oral vasodilators in “obliterative pulmonary hypertension”. All our patients improved clinically and subjectively and all increased their maximum oxygen consumption during exercise. This indicated that their improvement in cardiac output during the short term was sustained by the long term infusion. We believe that the symptomatic benefit of long term epoprostenol was due to its ability to increase cardiac output and tissue oxygenation; this resembles the mechanism of action of a response to oral hydralazine in patients with primary pulmonary hypertension. Exactly how the increase in cardiac output is achieved remains uncertain but even in the absence of a fall in pulmonary artery pressure it probably represents some decrease in the obstruction of the pulmonary vasculature. The mechanism is analogous to that which operates when vasodilators are given to patients with left ventricular dysfunction when reduction in afterload is accompanied by an increase in cardiac output rather than a fall in systemic arterial pressure. In both instances a fall in systemic arterial pressure resulting from a fall in systemic vascular resistance is counteracted by reflex increase in stroke volume.

The reason why all our patients responded both in the short term and in the long term is probably because we were able to reach the optimum vasodilating dose with the epoprostenol infusion; this is much more difficult to achieve with oral vasodilators.

Even when a clinical diagnosis of primary pulmonary hypertension has been made after extensive investigations including pulmonary angiography, other studies of necropsy specimens have shown that up to 60% of patients have evidence of recurrent pulmonary thromboembolism. This was also seen in three of our six patients in whom the results of histological examination were available (patients 2, 3, and 10). In all of them pulmonary angiograms had excluded major vessel obstruction. Their short term and long term responses were similar to those in patients with classic plexiform pulmonary arteriopathy. It could be argued that the thrombi occurred in situ; however, in our group of patients the sex ratio is not typical of the usually recognised condition.

Some evidence suggests that anticoagulation may prolong survival but most physicians believe that anticoagulants are useful only in preventing the secondary thromboembolism associated with low cardiac output. As well as being a vasodilator, epoprostenol is a powerful platelet antiaggregator and if abnormal platelet behaviour was important in the pathogenesis of primary pulmonary hypertension this effect might be an added benefit of the treatment. Tests of platelet function in patients on epoprostenol infusions, however, showed an “infusion” rebound of platelet activation starting at 2–4 days, reaching a maximum at 6–10 days, and then levelling off. No clinical complication of this enhanced platelet activation was seen in our patients. Nor have they been reported after short term infusions of epoprostenol for peripheral vascular disease. This phenomenon should be further explored, in particular with reference to clinical complications.

Epoprostenol had a positive clinical benefit in all our patients and all but one became mobile and went home. This improvement was achieved by treating the effects rather than the cause of primary pulmonary hypertension. Treatment did not reverse the
underlying disease process as its effects were not sustained in all patients. The two patients who died had the lowest pulmonary arterial oxygen saturation at the outset. It had no effect on the pulmonary pathology of the one patient whose lungs were examined before and after epoprostenol and in whom stopping the infusion had caused a rapid deterioration in clinical condition.

Treatment with epoprostenol improved the quality of life and the exercise tolerance in patients with a severe deteriorating disease who had not been helped by oral vasodilators. We believe that despite the problems of maintaining an intravenous infusion and the expense, this is a treatment that can be used in patients awaiting heart-lung transplantation when there may be a long wait for a suitable donor. A formal controlled study will be necessary, however, if epoprostenol infusion is to be considered for more general use in less severely affected patients with primary pulmonary hypertension.

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