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 16 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 septicaemia 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. 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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Table 1 Data on 10 patients with primary pulmonary hypertension

Patient	Sex	Age (yr)	Duration of symptoms (months)	Time since diagnosis (months)	Clinical severity of disability	Drug treatment		Biopsy specimen
1	F	28	78	8	Confined to hospital ward	Spironolactone Frusemide Continuous oxygen Warfarin	100 mg daily 160 mg daily	Plexogenic arteriopathy
2	F	38	16	12	Confined to hospital ward	Digoxin Spironolactone Frusemide Bendrofluazide Oxygen Warfarin	100 mg daily 80 mg daily 5 mg daily 18 h/day	Thrombotic pulmonary hypertension
3	F	21	14	10	Unable to walk 300 m	Warfarin		Thrombotic pulmonary hypertension
4	F	38	60	4	Unable to walk 200 m	Bumetanide Oxygen at night Warfarin	2 mg daily	Plexogenic arteriopathy
5	F	39	12	2	Unable to climb one flight of stairs	Nil		Plexogenic arteriopathy
6	M	24	16	1.5	Unable to walk 100 m	Digoxin Warfarin Cyclopenthiiazide	0.1 mg daily	NA
7	M	17	23	3	Confined to a wheelchair	Digoxin Disopyramide Warfarin		NA
8	F	32	48	40	Confined to a wheelchair	Oxygen Digoxin Frusemide Warfarin	80 mg daily	NA
9	M	34	5	1	Unable to walk 300 m	Warfarin		NA
10	M	32	31	27	Unable to walk 50 m	Frusemide Amiloride Warfarin	80 mg daily 10 mg daily	Thrombotic pulmonary hypertension

NA, not available.

with intravenous epoprostenol¹¹ 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 cath-

eterisation. 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 anti-coagulants, 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 2 Details of previous vasodilator treatment and its effect

Patient	Drug	Daily dose (mg)	Route	Duration	Effect
1	Hydralazine	50	Oral	2 days	Stopped due to syncope
	Nifedipine	60	Oral	6 weeks	No subjective improvement
	Isosorbide	20	Oral	6 weeks	No subjective improvement
2	Nifedipine	10	Oral	1 dose	No reduction in PVR
	Diazoxide	300	Into PA	1 dose	No reduction in PVR
3	Hydralazine	50	Oral	1 day	Stopped due to nausea
	Nifedipine	30	Oral	4 weeks	No subjective improvement
4	Glyceryl trinitrate	0.5	Sublingual	1 dose	Reduced PVR by 37%
	Nifedipine	10	Oral	1 dose	Reduced PVR by 12%
	Nifedipine	60	Oral	4 weeks	No subjective improvement
5	Hydralazine	400	Oral	4 weeks	No increase in exercise tolerance Caused eosinophilia
6	Diazoxide	150	Oral	1 dose	No reduction in PVR
	Diazoxide	300	Oral	1 day	Stopped due to syncope
7	Captopril	150	Oral	18 weeks	No subjective improvement
8	Pirbuterol	15	Oral	1 dose	No reduction in PVR
	Pirbuterol	45	Oral	13 weeks	No subjective improvement
9	Nifedipine	30	Oral	4 weeks	No subjective improvement
10	Captopril	150	Oral	10 weeks	No objective increase in exercise tolerance

PA, pulmonary artery; PVR, pulmonary vascular resistance.

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 Radiometer, Copenhagen, Denmark) and cardiac output (CO) by thermodilution 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) = CO surface area (l/min/m²)

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

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

O₂ content =
$$\frac{\text{O}_2 \text{ saturation} \times \text{O}_2 \text{ capacity}}{100} + \text{dissolved}$$

where O₂ capacity = Hb (g/dl) × 1.36

Peripheral O₂ delivery =
$$\text{arterial O}_2 \text{ content} \times \text{CO (ml/min)}$$

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

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)

	Previous catheterisation	Our catheterisation	P value
PAP (10) (mm Hg)	66 (6)	76 (6)	<0.02
PVR (6) (dyn s cm ⁻⁵)	1354 (200)	1634 (225)	<0.005
Pao ₂ (5) saturation(%)	62 (2)	49 (3)	<0.001
CI (5) (l/min/m ²)	2.2 (0.2)	1.8 (0.2)	<0.005

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.¹² The maximum walking speed (WS) attained in km/h and the maximum oxygen consumption attained in ml/kg/min ($\dot{V}$ 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

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

Patient	Max dose of epoprostenol	SAP (mm Hg)	PAP (mm Hg)	CI (l/min/m ²)	PVR (dyn s cm ⁻⁵)	SVR (dyn s cm ⁻⁵)	HR (beats/min)	Pao ₂ saturation	O ₂ delivery (ml/kg/min)
1	Baseline	78	100	1.7	2133	1600	104	45	5.8
	4 ng/kg/min	77	81	2.3	1190	1200	120	50	8.2
2	Baseline	82	71	1.5	1899	1992	70	38	—
	6 ng/kg/min	66	68	1.9	1365	1223	82	45	—
3	Baseline	80	55	1.7	1376	1952	98	52	10.9
	5 ng/kg/min	65	65	1.8	1629	1425	104	53	11.9
4	Baseline	83	80	2.1	1558	1684	87	60	9.5
	4 ng/kg/min	75	80	2.6	1242	1174	90	70	11.6
5	Baseline	73	62	3.0	784	1094	90	51	15.2
	4 ng/kg/min	72	48	3.1	580	1020	90	61	16.8
6	Baseline	93	60	1.5	1583	2187	77	42	8.5
	6 ng/kg/min	80	60	1.8	1358	1457	84	56	9.5
7	Baseline	100	80	1.8	1800	2275	78	51	12.4
	6 ng/kg/min	80	80	2.1	1516	1579	82	57	14.3
8	Baseline	70	50	2.2	869	1440	63	60	11.8
	6 ng/kg/min	61	48	2.8	675	1031	68	68	15.1
9	Baseline	95	105	1.5	2744	2425	84	43	8.3
	8 ng/kg/min	70	105	2.0	2054	1340	96	57	10.9
10	Baseline	76	93	1.3	2523	1723	82	42	7.3
	6 ng/kg/min	62	98	1.45	2400	1048	82	51	8.1
Mean	Baseline	83 (3)	76 (6)	1.83 (0.2)	1727 (202)	1837 (129)	83 (4)	48 (2)	10.0 (1)
(SEM)	5.5 ng/kg/min	71 (2)	73 (6)	2.19 (0.2)	1401 (175)	1250 (61)	90 (4)	57 (2)	11.8 (1)
p value		<0.001	>0.4	<0.005	<0.02	<0.001	<0.005	<0.001	<0.001

SAP, systemic arterial pressure; PAP, pulmonary artery 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.

Fig 1 Individual exercise tolerances expressed as maximum oxygen consumption at various times before and after starting epoprostenol. $\uparrow$ Epoprostenol started.

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

Fig 2 Duration of epoprostenol treatment and subjective effects of epoprostenol and final outcomes in individual patients. Length of time that subjective benefit was present is indicated by cross hatching. Numbers in parentheses show maximum dose of epoprostenol (ng/kg/min).

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 septicaemia, 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 septicaemia 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 anti-nuclear 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.¹³ 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 arterioles 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%.⁴ 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.¹⁴ In the early stages of the disease the vasoconstriction is labile and responsive to vasodilators but later it becomes fixed and irreversible.¹⁵ 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.¹⁶ 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.^{7 17} The administration of vasodilators with long half lives can also cause profound systemic hypotension that is resistant to treatment and can lead to death.^{8 9} Epoprostenol is a powerful vasodilator when it is administered intravenously. It has a rapid onset of action that is dose dependent.¹⁰ 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.¹⁰ Some workers have claimed that in order to establish a pulmonary vasodilatation effect, there should be a fall in pulmonary artery pressure and the pulmonary vascular resistance should decrease more than systemic vascular resistance.¹⁶ 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,¹⁸ however, and in primary pulmonary hypertension is associated with a significant morbidity and mortality⁴ 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.¹⁹ 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 subjects²⁰ and patients with left heart failure.²¹ A recent paper has recommended its use also in assessing the response to oral vasodilators in "obliterative pulmonary hypertension".²² 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.^{23 24} 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.²⁵ 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.^{4 14} 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 survival⁴ but most physicians believe that anticoagulants are useful only in preventing the secondary thromboembolism associated with low cardiac output.²⁶ 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 "intra-infusion" rebound of platelet activation starting at 2-4 days, reaching a maximum at 6-10 days, and then levelling off.²⁷ 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.

We thank Dr Derek Wheeldon for his expert technical assistance and Dr Pete Stovin for his opinion on the histological sections. We are also grateful to the Wellcome Foundation Ltd for their kind support. Dr Jones is a British Heart Foundation Research Fellow.

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