

Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost

T W Higenbottam, A Y Butt, A T Dinh-Xaun, M Takao, G Cremona, S Akamine

Abstract

Objective—To compare prostacyclin with an analogue, iloprost, in treatment of severe pulmonary hypertension.

Patients—Eight patients with severe pulmonary hypertension: primary in five, thromboembolic pulmonary hypertension in three.

Methods—All patients underwent right heart catheterisation. Mean (SEM) right atrial pressure was 9.9 (2.2) mm Hg, mean pulmonary artery pressure 67.4 (3.0) mm Hg, cardiac index 1.75 (0.13) l/min/m² and mixed venous oxygen saturation 59.1(3.1)%. Continuous intravenous epoprostenol (prostacyclin, PGI₂) or iloprost was given for phase I (three to six weeks); the patients were then crossed over to receive the alternate drug in an equivalent phase II.

Main outcome measures—Exercise tolerance was measured at baseline and at the end of phase I and II with a 12 minute walk; distance covered, rest period, percentage drop in arterial oxygen saturation (Δ SaO₂%) and percentage rise in heart rate (Δ HR%).

Results—Walking distance covered rose from (mean (SEM)) 407.5 (73) to 591 (46) m with PGI₂ ($p = 0.004$) and to 602.5 (60) m while on iloprost ($p = 0.008$). Rest period decreased from 192 (73) seconds at baseline to 16 (16) seconds with PGI₂ ($p = 0.01$) and to 58 (34) seconds with iloprost ($p = 0.008$). Δ HR% was 37.5(6)% at baseline, 35(3)% on PGI₂, and 24(6)% on iloprost ($p = 0.04$).

Conclusions—Both intravenous PGI₂ and iloprost caused significant improvement in exercise tolerance. Iloprost offers an alternative to PGI₂ treatment of severe pulmonary hypertension.

(Heart 1998;79:175-179)

Keywords: prostacyclin; vasodilatation; iloprost; pulmonary hypertension

Primary pulmonary hypertension is a serious disease with a fatal outcome in a majority of patients.¹⁻³ Calcium channel blockers^{4,5} together with anticoagulants¹ have been used to treat mild to moderate disease, while in severe pulmonary hypertension continuous prostacyclin infusion has been shown to improve patients' wellbeing as well as survival.⁶⁻⁸ However, prostaglandin I₂ (prostacyclin, PGI₂) has a short half life of less than five minutes in

vivo and is therefore quite unstable. It has to be protected from light and needs to be dissolved in a glycine buffer for intravenous administration.⁹⁻¹¹ Iloprost is a more stable synthetic analogue of PGI₂.¹² It is a comparable pulmonary vasodilator to PGI₂ and therefore has potential for the treatment of pulmonary hypertension.¹³ In this prospective study we have compared the effects of iloprost and PGI₂ on exercise capacity in patients with severe pulmonary hypertension.

Methods

The study involved eight patients (four men and four women) diagnosed as having either primary ($n = 5$) or thromboembolic ($n = 3$) pulmonary hypertension, who had had symptoms for an average of 44.6 months and were categorised into New York Heart Association (NYHA) grade III to IV disability. Dyspnoea was the main symptom in all patients, five having chest pain and one syncope. In one patient the onset of symptoms was associated with pregnancy, while in another patient the presentation was Raynaud's syndrome.

The diagnosis of primary pulmonary hypertension was made after excluding other causes of pulmonary hypertension,¹⁴ and thromboembolic disease was diagnosed by lung scan showing one or more normally ventilated segmental or subsegmental perfusion defects.¹⁵ Four patients were already taking anticoagulants, five were on calcium channel blockers, and three were on both warfarin and calcium channel blocker treatment (table 1). On entry to the study, all patients stopped taking oral vasodilators and calcium channel blockers, but continued anticoagulants.

The study was approved by the local ethics committee and all patients signed informed consent. Ten patients initially participated, but two were subsequently excluded as they could not comply with the study protocol.

RIGHT HEART CATHETERISATION

All patients had right heart catheterisation. Anticoagulant treatment was stopped before the procedure and written consent was obtained. A triple lumen, flow directed catheter was inserted through the internal jugular vein under local anaesthesia while the patient was lying in a supine position. Mean right atrial pressure, pulmonary arterial pressure, and pulmonary artery wedge pressure values were obtained using electronic integration of the pressure signals, with the mid-axillary line as a zero reference point. Cardiac output was

Section of Respiratory Medicine, Department of Medicine and Pharmacology, School of Medicine, University of Sheffield, Sheffield, UK
T W Higenbottam
A T Dinh-Xaun
M Takao
G Cremona
S Akamine

Respiratory Physiology Department, Papworth Hospital, Cambridge, UK
A Y Butt

Correspondence to: Professor Higenbottam, Director, Division of Clinical Science (CSUHT), University of Sheffield, Floor F, Medical School, Beech Hill Road, Sheffield S10 2RX, UK.

Accepted for publication 1 October 1997

Table 1 Characteristics of the patients and anthropometric data

Patient	Age (years)	Sex	Height (cm)	Weight (kg)	Diagnosis	NYHA grade	Duration of symptoms (months)	Treatment before the study
1	48	M	181	86	TEPH	IV	36	Dilt, Warf
2	21	F	167	62	PPH	III	36	Oxy, Nif, War
3	47	M	180	88	PPH	III	60	Frum, Dilt, War
4	38	M	174	90	TEPH	IV	60	Etha, Amil, Nicard, Pirb
5	54	F	158	83	PPH	IV	20	Frum, Dilt
6	41	M	186	75	TEPH	III	120	Bum, Amil, War, Pred,
7	38	F	157	55	PPH	III	13	Pred
8	20	F	161	49	PPH	III	12	War

Amil, amiloride; Bum, bumetanide; Dilt, diltiazem; Etha; ethacrynic acid; Fru, frumil; Nic, nicardipine; Pirb, pirbuterol; War, warfarin; PPH, primary pulmonary hypertension; Pred, prednisolone; TEPEH, thromboembolic pulmonary hypertension.

measured by thermodilution technique using a bedside cardiac output computer (American Edwards Laboratory, Santa Ana, California, USA). Pulmonary vascular resistance (mean pulmonary artery pressure minus pulmonary artery wedge pressure divided by cardiac output) was calculated in Wood units (wu). Cardiac rhythm was monitored using continuous electrocardiography, and arterial pressure was monitored from a radial artery cannula. Blood samples were obtained from pulmonary and radial arteries for gas tension analysis.

ACUTE VASODILATOR TRIAL

After obtaining baseline measurements, an intravenous PGI₂ infusion was started at an initial dose of approximately 2 ng/kg/min, which was then increased stepwise after five to 15 minutes by 1 to 2 ng/kg/min. Epoprostenol (prostacyclin, PGI₂) was supplied by Wellcome Foundation (Beckenham, Kent, UK) as a sodium salt which was dissolved in an accompanying glycine buffer before diluting it in normal saline. All the haemodynamic measurements and blood samples were obtained before increasing the dose. This acute vasodilator study was continued until there was a 20% reduction in pulmonary vascular resistance or a fall of systolic systemic blood pressure below 100 mm Hg. As it takes five minutes for PGI₂ to be inactivated,¹⁶ twenty minutes were allowed after stopping PGI₂ before starting the intravenous infusion of iloprost. The order was chosen because iloprost has a half life of over 13 minutes.¹⁵ Iloprost (supplied by Schering Healthcare, Burgess Hill, Sussex, UK) was available in 1 ml ampoules containing 100 µg of the drug in sterile physiological saline with the addition of Tris buffer (pH 8.3) and

ethanol (1%). This was diluted in normal saline to prepare the intravenous infusion. Iloprost infusion was started at approximately 1 to 2 ng/kg/min and increased in a stepwise fashion according to the protocol as for PGI₂. Haemodynamic measurements and blood samples were taken every five to 15 minutes before increasing the dose.

LONG TERM TREATMENT

After the right heart catheterisation, patients were allocated for phase I of the study infusion (either PGI₂ or iloprost), given through an indwelling central line. The syringe containing the solution was driven by an electric pump which was carried by the patients in a small shoulder holster and did not restrict their mobility. The pump was protected from light, and the patients were taught the aseptic technique of preparing the solution, as well as the storage, administration, and maintenance of the infusion, which they were able to do independently at home. At the end of phase I, patients crossed over to phase II (the alternative treatment). The duration of PGI₂ and iloprost infusion varied for individual patients (range 4 to 19 weeks for PGI₂ and 3.5 to 11 weeks for iloprost); on average both PGI₂ and iloprost were given for seven weeks. It was intended to keep the duration of both phase I and phase II to four weeks but this could not be achieved. (The variation in the treatment duration occurred because patients were referred from other centres and at times they had to travel long distances; therefore follow up periods were kept flexible.) Exercise tolerance was measured at baseline while patients were on their previous treatments, and then at the end of each phase using a monitored 12 minute

Table 2 Baseline right heart catheter data for patients and results of acute infusion of either prostacyclin or iloprost

Patient	Diagnosis	Baseline					Epoprostenol					Iloprost						
		mRAP	mPAP	CI	PVR	SvO ₂	mRAP	mPAP	CI	PVR	SvO ₂	Dose	mRAP	mPAP	CI	PVR	SvO ₂	Dose
1	TEPH	15	60	1.7	12.8	46	14	58	2.1	10.2	60	6.2	—	—	—	—	—	—
2	PPH	5	69	1.6	16.6	57	5	68	2.0	13.5	65	6.4	4	64	2.1	14.2	66	9.7
3	PPH	11	55	2	10.8	66	9	44	2.3	8.0	76	6.1	9	44	2.4	8.2	72	3.0
4	TEPH	6	66	1.7	15.5	55	5	58	2.4	9.1	57	4.4	5	52	2.8	7.1	58	6.7
5	PPH	18	68	1.9	—	52	13	49	2.7	—	71	6.4	14	53	2.7	—	64	4.8
6	TEPH	17	67	1.2	—	58	13	—	1.6	—	65	5.3	—	—	—	—	—	—
7	PPH	4	70	1.5	25.2	65	7	74	1.7	—	64	7.3	8	79	1.9	—	73	10.9
8	PPH	3	84	2.4	21.1	74	1	77	3.4	14.2	72	8.2	—	69	3.7	11.7	—	8.2
Mean		9.9	67.4	1.7	17.0	59.1	8.4	61.1*	2.3*	11.0*	66.2*	6.3	6.7	59.7*	2.6*	10.3	66.6*	7.2
SEM		(2.2)	(3.0)	(0.1)	(2.2)	(3.1)	(1.7)	(4.7)	(0.2)	(1.2)	(2.2)	(0.4)	(2.0)	(5.1)	(0.2)	(1.6)	(2.7)	(1.3)

*p < 0.05.

CI, cardiac index (l/min/m²); mRAP, mean right atrial pressure (mm Hg); mPAP, mean pulmonary artery pressure (mm Hg); PVR, pulmonary vascular resistance; SvO₂, mixed venous oxygen saturation (%); PPH, primary pulmonary hypertension; TEPEH, thromboembolic pulmonary hypertension.

Table 3 Twelve minute walk data at baseline

Patient	Diagnosis	Distance (m)	Rest (s)	ΔSaO ₂ (%)	ΔHR (%)
1	TEPH	280	0	3.1	31.3
2	PPH	560	85	3.2	63.7
3	PPH	570	165	16.9	25.6
4	TEPH	180	420	4.2	19.5
5	PPH	120	360	31.8	14.9
6	TEPH	380	505	7.7	49.5
7	PPH	720	0	—	56.4
8	PPH	450	0	49.4	38.8
Mean (SEM)		407.5 (73)	192 (73)	16.6 (6.7)	37.5 (6.3)

ΔHR (%), percentage increase in heart rate; ΔSaO₂ (%), percentage drop in oxygen saturation; PPH, primary pulmonary hypertension; TEPH, thromboembolic pulmonary hypertension.

Table 4 Twelve minute walk data on epoprostenol (PGI₂)

Patient	Diagnosis	Distance (m)	Rest (s)	ΔSaO ₂ (%)	ΔHR (%)	Duration (weeks)	Dose PGI ₂ (ng/kg/min)
1	TEPH	360	0	—	—	19	5.5
2	PPH	620	0	11.1	41.3	7	20
3	PPH	680	0	—	—	4.5	6.3
4	TEPH	520	0	4.1	28.6	5	15.8
5	PPH	490	125	—	—	4	4
6	TEPH	700	0	4.3	42.5	4	3.8
7	PPH	760	0	3.1	26.8	5	6.9
8	PPH	600	0	—	35.8	7.5	7.3
Mean (SEM)		591** (46)	16* (16)	6 (1.8)	35 (3.2)	7 (1.8)	8.7 (2.2)

*p < 0.05, **p < 0.01 compared to baseline.

ΔHR (%), percentage increase in heart rate; ΔSaO₂ (%), percentage drop in oxygen saturation; PPH, primary pulmonary hypertension; TEPH, thromboembolic pulmonary hypertension.

walk.¹⁷ During the 12 minute walk, arterial oxygen saturation and heart rate were monitored. Duration of rest periods during the test was also recorded.

Of the two patients who were excluded from the initial cohort, one received only iloprost and was not willing to cross over to PGI₂ in phase II; the second patient was excluded from the analysis because his baseline exercise data were not available.

STATISTICAL ANALYSIS

Distance covered during the 12 minute walk was recorded in metres and the rest period was recorded in seconds. Heart rate (beats/min) was noted at rest and then at each minute interval. The difference between resting and maximum heart rate was calculated in percentage rise in heart rate (ΔHR%). Degree of oxygen desaturation was calculated as percentage fall in oxygen saturation (ΔSaO₂%), taking into account oxygen saturation at rest and minimum saturation during exercise. During right heart catheterisation mean right atrial and pulmonary artery pressures were recorded

Table 5 Twelve minute walk data on iloprost

Patient	Diagnosis	Distance (m)	Rest (s)	ΔSaO ₂ (%)	ΔHR (%)	Duration (weeks)	Dose PGI ₂ (ng/kg/min)
1	TEPH	420	0	0	0	3.5	2.1
2	PPH	740	0	2	50	6	2.7
3	PPH	880	0	—	—	8	1.0
4	TEPH	340	260	4.1	23.7	5	1.7
5	PPH	580	55	13.5	15.3	7	0.7
6	TEPH	580	150	6	20.8	11	1.6
7	PPH	640	0	1	27.1	8	3.4
8	PPH	640	0	46.9	32	7.5	3.9
Mean (SEM)		602.5† (60)	58† (34)	10.5* (6.3)	24.1* (5.8)	7 (0.8)	2.1‡ (0.4)

*p < 0.005, †p < 0.001 comparison with baseline; ‡p < 0.05 comparison with PGI₂ and iloprost dose.

ΔHR (%), percentage increase in heart rate; ΔSaO₂ (%), percentage drop in oxygen saturation; PPH, primary pulmonary hypertension; TEPH, thromboembolic pulmonary hypertension.

in mm Hg; cardiac output in l/min and cardiac index in l/min/m² of body surface area. Comparisons of exercise and haemodynamic data on PGI₂ and iloprost with respect to baseline were made using the paired Wilcoxon test. It was assumed that there was no carry over effect from phase I to phase II and the comparisons were based on the tests of the treatment results versus the baseline. Results are shown as mean with a standard error. A p value of less than 0.05 was regarded as statistically significant.

Results

ACUTE RESPONSE TO TREATMENT

Baseline measurements during right heart catheterisation indicated the severity of pulmonary hypertension (table 2). After a vasodilator challenge, there was no significant change in right atrial pressure, either with PGI₂ or iloprost: 9.9 (2.2) at baseline v 8.4 (1.7) mm Hg with PGI₂ and 6.7 (2.0) mm Hg with iloprost (table 2). The mean pulmonary artery pressure fell from 67.4 (3.0) to 61.1 (4.7) mm Hg with PGI₂ (p = 0.04) and to 59.7 (5.1) mm Hg with iloprost (p < 0.05), while cardiac index improved both with PGI₂ and iloprost (1.75 (0.1) l/min/m² at baseline to 2.3 (0.2) l/min/m² with PGI₂ (p = 0.004) and 2.6 (0.2) l/min/m² with iloprost (p = 0.02)). The pulmonary vascular resistance was not measured in some patients, because of difficulties in measuring either the pulmonary artery wedge pressure or the cardiac output. Where it was measured, there was a fall from baseline with both PGI₂ and iloprost: 17 (2.2) wu at baseline (n = 6) to 11 (1.2) wu with PGI₂ (n = 5, p = 0.03), and to 10.3 (1.6) wu with iloprost (n = 4). Mixed systemic venous oxygen saturation (Svo₂) improved with both drugs: 59.1(3.1)% at baseline to 66.25(2.2)% with PGI₂ (p < 0.05) and to 66.6(2.7)% with iloprost (p = 0.03) (table 2).

LONG TERM TREATMENT

All patients were able to perform a 12 minute walk test to assess exercise tolerance at baseline. There was an improvement in exercise tolerance, as judged by the distance covered and the duration of rest required during the walk test: 407.5 (73) m at baseline increasing to 591 (46) m with PGI₂ (p = 0.004) (tables 3 and 4), and to 602.5 (60) m with iloprost (tables 3 and 5) (p = 0.008). Rest periods required by the patients were less while on PGI₂ or iloprost: 192 (73) at baseline v 16 (16) seconds on PGI₂ (p = 0.02), and 58 (34) seconds on iloprost (p = 0.008). There was a trend towards less oxygen desaturation (ΔSaO₂%) during exercise while on PGI₂ and iloprost compared with baseline; however, data availability was restricted because of the low peripheral perfusion in some patients, which caused difficulty in measuring transcutaneous oxygen saturation: 16.6(6.7)% O₂ desaturation at baseline (n = 7) v 6(1.8)% with PGI₂ (n = 4) and 10.5(6.3)% with iloprost (n = 7) (p = 0.02). The ΔHR% during exercise was 37.5(6.3)% at baseline

(n = 8) compared with 35(3.2)% while on PGI₂ (n = 5), and 24.1(5.8)% while on iloprost (n = 7) (p = 0.04) (tables 3, 4, and 5).

Discussion

In this study we have shown the effect of a PGI₂ analogue, iloprost, on exercise tolerance of patients with pulmonary hypertension. While on iloprost, the improvement in the distance covered during the 12 minute walk was more than 200 m. This, in conjunction with the reduced rest period required during the exercise test, suggests that these patients would have experienced enhancement in their daily activities. The number of patients studied is small but provides evidence that iloprost may improve the exercise capacity of patients with severe pulmonary hypertension. Similar results have been reported in patients with systemic sclerosis and pulmonary hypertension.¹⁸

Iloprost has a similar molecular structure to PGI₂ and works through PGI₂ receptors present on the vascular endothelial cells.^{19, 20} Similar in function to PGI₂, it is a potent vasodilator of the pulmonary vascular bed¹³ and also inhibits platelet aggregation.¹⁸ It is a relatively more stable compound than PGI₂.¹² It can be dissolved in isotonic solution, does not have to be protected from light, and can be stored at room temperature.

The haemodynamics were not uniform in all patients. Right atrial pressure, cardiac index, and mixed Svo₂ have prognostic value and varied in the subjects studied. In five patients the mean right atrial pressure was below 10 mm Hg, while in the other three it was in excess of 10 mm Hg. In patients 3 and 8, the cardiac index was 2 and 2.4 l/min/m² respectively, while in six other patients it was below 2 l/min/m², suggesting marked right ventricular dysfunction.² However, the majority of patients had an Svo₂ of less than 63%, suggesting severe disease,¹ and all were severely disabled, being categorised into NYHA grade III-IV, which is also associated with a poor prognosis.⁷

It may also be argued that there was no washout period between PGI₂ and iloprost, allowing carry over effects of the first treatment. However PGI₂ has a short half life of minutes¹⁶ and it is unlikely that vasodilator activity would have lasted for any significant period on changing from phase I to phase II of the study. There was an ethical reason for not having a washout with a placebo between phase I and II: as the subjects had a potentially fatal disease, there was a risk of causing a rapid haemodynamic and symptomatic deterioration on stopping potent vasodilator treatment.

Five patients had PGI₂ and three had iloprost in phase I. After crossover to the alternative drug there was no worsening of symptoms and the improvement of exercise tolerance in each patient was generally maintained. In two patients there was a slight decline in the 12 minute walk distance on switching from PGI₂ to iloprost, and two patients decreased their walking distance slightly on changing from iloprost to PGI₂. However, the duration of rest required during the 12 minute walk did not

increase for any of these patients. Notably, all five patients who were on calcium channel blockers at baseline improved their exercise tolerance while on iloprost.

As this is a short term study involving eight patients, it may be necessary to conduct a long term survival study to evaluate the therapeutic role of iloprost fully. However, these early data suggest that the prostacyclin analogue iloprost may be an effective long term treatment for severe pulmonary hypertension, and it is generally well tolerated—headaches, diarrhoea, and abdominal pain may occur initially but usually settle after 24 to 48 hours. There is some evidence that this analogue of PGI₂ may be a little more stable, with an in vivo half life of approximately 13 minutes,¹² compared with five minutes for PGI₂. At present it has to be given as a continuous intravenous infusion through a central line, which may occasionally create problems such as infection, blockage, and displacement of the line. Finally iloprost is approximately twice as strong a vasodilator as PGI₂—only half the dose is required to produce the same long term effects. This might reduce the already high cost of these drugs.

CONCLUSION

We have shown that the synthetic prostacyclin analogue iloprost may improve the exercise tolerance of patients with severe pulmonary hypertension. Its effect on long term survival in pulmonary hypertension is, however, not known. Its therapeutic efficacy would probably need to be further evaluated in a larger survival study.

We are grateful to Schering Health Care Ltd for providing us with the supply of iloprost, as well as for the patients' travel grants.

- 1 Fuster V, Steele PM, Edwards WD, et al. Primary pulmonary hypertension: natural history and importance of thrombosis. *Circulation* 1984;70:580-7.
- 2 D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. *Ann Intern Med* 1991;115:343-9.
- 3 Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107:216-23.
- 4 Rich S, Brundage BH. High dose calcium channel blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation* 1987;76:135-41.
- 5 Rich S, Kaufmann E, Levy P. The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327:76-81.
- 6 Jones DK, Higenbottam TW, Wallwork J. Treatment of primary pulmonary hypertension with intravenous epoprostenol (prostacyclin). *Br Heart J* 1987;57:270-8.
- 7 Higenbottam TW, Spiegelhalter D, Scott J, et al. Prostacyclin (epoprostenol) and heart-lung transplantation as treatments of severe pulmonary hypertension. *Br Heart J* 1993;70:366-70.
- 8 Butt AY, Cremona G, Sharples L, et al. Continuous infusion of prostacyclin (PGI₂) improves survival in severe pulmonary hypertension [abstract]. *J Am Coll Cardiol* 1995; (suppl):221A.
- 9 Barst R, Rubin L, Long W, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;334:296-301.
- 10 Higenbottam T. The place of prostacyclin in the clinical management of primary pulmonary hypertension. *Am Rev Respir Dis* 1987;136:782-5.
- 11 Barst RJ, Rubin LJ, McGoon MD, et al. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994;121:409-15.
- 12 Kaukinen S, Ylitalo P, Pessi T, Vapaatalo H. Hemodynamic effects of iloprost, a prostacyclin analog. *Clin Pharmacol Ther* 1984;36:464-9.
- 13 Scott JP, Higenbottam TW, Wallwork J. The acute effect of the synthetic prostacyclin analogue iloprost in primary pulmonary hypertension. *Br J Clin Pharmacol* 1990;6:231-4.

- 14 Butt AY, Higenbottam TW. Primary pulmonary hypertension. In: Jackson G, ed. *Difficult concepts in cardiology*. London: Martin Dunitz, 1994:215–43.
- 15 Hull RD, Raskob GE, Heish J. The diagnosis of a clinically suspected pulmonary embolism. Practical approaches. *Chest* 1986;**89**(suppl):417–25.
- 16 Haslam RJ, McClenaghan MD. Measurement of circulating prostaglandin. *Nature* 1981;**292**:364–7.
- 17 McGavin CR, Gupta SP, McHardy GJR. Twelve minute walking test for assessing disability in chronic bronchitis. *BMJ* 1976;**ii**:822–3.
- 18 De Mata LJ, Gomez-Sanchez MA, Aranzana M, et al. Long-term iloprost infusion therapy for severe pulmonary hypertension in patients with connective tissue disease. *Arthritis Rheum* 1994;**37**:1528–33.
- 19 Schror K, Darius H, Matzky R, et al. The anti platelet and cardiovascular actions of a new carbacyclin derivative (ZK36374)—equipotent to PGI₂ in vitro. *Arch Pharmacol* 1981;**316**:252–5.
- 20 Bugiardini R, Galvani M, Ferrini D, et al. Effects of iloprost, a stable prostacyclin analog, on exercise capacity and platelet aggregation in stable angina pectoris. *Am J Cardiol* 1986;**58**:453–9.