

Haemodynamic effects of prostacyclin (PGI₂) in pulmonary hypertension

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SUMMARY An infusion of prostacyclin (PGI₂) in four patients with pulmonary hypertension resulted in a dose-related decrease in the systemic and pulmonary vascular resistance and an increase in cardiac output. No selectivity for the pulmonary vasculature was observed and the drug was not therapeutically beneficial.

Pulmonary hypertension may result from parenchymal lung disease, some cardiac diseases, or pulmonary thromboembolism.

Idiopathic pulmonary hypertension is a rare disorder of the pulmonary vasculature. The cause is unknown and three pathological entities are described: veno-occlusive disease, recurrent pulmonary thromboembolism, and plexigenic pulmonary arteriopathy.¹ The treatment of pulmonary hypertension is largely ineffective and the prognosis uniformly bad, though occasional case reports of long-term survival² and even the regression of the disease have been recorded.³

Initially the treatment consisted of anticoagulants. These, however, did not appear to alter the natural history of the disease or the survival time.⁴ Oral diazoxide treatment has been helpful in some patients⁵ with this condition as have isoprenaline,⁶ 7 phentolamine,⁸ and oxygen.⁹ Verapamil has been reported to cause slight lowering of the pulmonary arterial pressure in pulmonary hypertension resulting from a variety of causes,¹⁰ as has PGE₁.¹¹

Prostacyclin (PGI₂) is a metabolite of arachidonic acid produced by an enzyme isolated from the blood vessel walls.¹² Recent reports suggest that the cat lung spontaneously releases a substance similar to PGI₂¹³ and that PGI₂ lowers lobar vascular resistance¹⁴ leading to the hypothesis that a similar substance is involved in the modulation of vasoconstrictor stimuli in the lung.¹⁴ An infusion of PGI₂ completely reversed the vasoconstriction of the pulmonary vasculature in a neonate with persistent fetal circulation,¹⁵ but to our knowledge it has not been used in adults with pulmonary hypertension. This preliminary communication reports the

haemodynamic effects of a prostacyclin infusion in four adults with pulmonary hypertension primarily on the basis of pulmonary vascular disease.

Subjects and methods

CASE 1

A 30-year-old female gravida 3, para 3, presented three weeks after delivery with a two-year history of progressive shortness of breath which increased considerably during the puerperium. On examination she was not cyanosed and was not in heart failure but had a loud palpable pulmonary second sound and a right-sided third heart sound. Her respiratory function tests were slightly abnormal, with changes suggesting small airways disease. She had right ventricular hypertrophy on the electrocardiogram and the chest x-ray showed a dilated pulmonary artery trunk, a finding that was also present on a film taken elsewhere two years earlier.

CASE 2

A 60-year-old man presented with a four year history of shortness of breath that had deteriorated recently. The dyspnoea was purely exertional and he denied any dyspnoea at rest or orthopnoea. He had a loud pulmonary second sound, right ventricular hypertrophy on electrocardiogram, and a dilated main pulmonary artery segment on chest x-ray. Respiratory function tests were similar to case 1, with changes suggestive of subclinical small airways disease.

CASE 3

A 60-year-old man with a two week history of exertional dyspnoea with no orthopnoea or chest pain, whose past history included two previous

hospital admissions in 1972 and 1974, respectively, with pleuritic chest pain and haemoptysis: no explanation was found for these episodes and his symptoms rapidly resolved without specific treatment.

He had a loud pulmonary second sound without a right ventricular heave or signs of right heart failure. There was no cardiomegaly on chest *x*-ray but his electrocardiogram was consistent with right ventricular hypertrophy. The lung scan showed numerous nonsegmental areas of hypoperfusion in both lungs and the only abnormality on respiratory function tests was a slight reduction in his maximum mid-expiratory flow rate. Shortly after admission he developed a painful right leg and subsequent venography showed an extensive deep vein thrombosis in his right calf.

CASE 4

A 50-year-old woman with a one year history of breathlessness on exertion with some cough and sputum had been treated recently for angina pectoris with beta-blockers but these gave her Raynaud's phenomenon and aggravated her breathlessness. On examination she had low pitched

rhonchi at both lung bases, a right ventricular heave, and a loud unsplit second heart sound. Her electrocardiogram was consistent with right ventricular hypertrophy and on chest *x*-ray there was a moderate dilatation of the main pulmonary artery segment. On a chest *x*-ray in 1969 this segment was prominent but not as dilated as at this admission. Respiratory function tests showed normal blood gases and normal vital capacity with a FEV₁ 1.0/VC of 0.51, which was unresponsive to bronchodilators.

Pulmonary arterial pressures were measured continuously via a 7.5F Swan Ganz catheter and a Statham P23DL transducer. Systemic arterial pressure was recorded via an intra-arterial cannula and Statham transducer. The cardiac output was obtained by the thermal dilution technique using ice cold 5 per cent dextrose as indicator and an Edwards Laboratory cardiac output computer. Prostacyclin as a dilute solution (4000 ng/ml) at 5°C was infused via the right atrial port of the Swan Ganz catheter.

Results

In each of these patients pulmonary angiography did not detect any obstructed major branches or

Table Haemodynamic effects of PGI₂

Case no.	PGI ₂ rate (ng/kg per min)	Systemic blood pressure		Pulmonary artery pressure		Cardiac output (l/min)	Systemic* resistance	Pulmonary resistance†	Resistance ratio‡
		S/D (mmHg)	Mean (mmHg)	S/D (mmHg)	Mean (mmHg)				
1	—	120/77	92	89/62	74	2.77	29.6	25.3	0.855
	0.44	106/70	82	88/52	65	—	—	—	0.897
	0.64	92/50	65	98/55	69	—	—	—	1.19
	§	63/35	49	73/47	56	—	—	—	1.33
	—	141/77	100	86/36	53	3.01	31.8	16.9	0.531
	4	105/54	77	78/30	46	3.48	20.4	12.7	0.621
	8	130/65	88	65/22	39	3.45	24.3	10.7	0.454
2	16	122/60	80	76/27	45	3.58	21.2	12.0	0.566
	16	75/41	63	59/23	36	3.80	15.5	8.94	0.577
	—	125/62	80	53/21	33	5.82	13.1	5.50	0.421
	2	131/64	81	48/14	23	—	—	—	0.286
	4	139/64	90	45/10	21	5.84	14.7	3.43	0.233
3	8	124/62	75	44/11	20	—	—	—	0.257
	16	118/54	70	41/8	18	6.29	10.5	2.70	0.258
	—	134/53	80	48/11	26	7.26	10.5	3.58	0.342
4	2	107/45	66	43/11	24	—	—	—	0.378
	4	110/46	65	41/15	24	9.36	6.52	2.56	0.393
	8	102/42	64	34/9	22	10.65	5.63	2.06	0.367
	16	107/42	65	34/9	22	10.42	5.85	2.11	0.361
	16¶	90/38	54	27/8	20	—	—	—	0.400

$$\text{*Systemic resistance} = \frac{(\text{Mean systemic pressure} - \text{right atrial pressure})}{\text{Cardiac output}}$$

Where the right atrial pressure was constant at 10 mmHg in case 1, and 4 mmHg in cases 2, 3, and 4.

$$\text{†Pulmonary resistance} = \frac{(\text{Mean pulmonary artery pressure} - \text{wedge pressure})}{\text{Cardiac output}}$$

The wedge pressure remained constant at 2, 1, and 0 mmHg in cases 2, 3, and 4, respectively. It could not be measured in case 1 and a value of 10 mmHg has been assumed.

$$\text{‡Resistance ratio} = \frac{(\text{Pulmonary resistance})}{(\text{systemic resistance})} = \frac{(\text{Pulmonary pressure drop})}{(\text{systemic pressure drop})}$$

§Bolus of 4 ng/kg.

¶After the infusion at this rate had been continued for 30 minutes.

filling defects within these branches. Intracardiac shunts were excluded by measurement of oxygen saturation and dye dilution curves. Pulmonary arterial pressures were raised in all four cases and are listed in the Table. The pulmonary artery wedge pressure was recorded in three of the cases and was within normal limits. Case 1 was too ill to risk wedging the pulmonary artery catheter but an echocardiogram showed a normal mitral valve and left ventricle, implying that the left atrial pressure was probably normal. Prostacyclin was infused at the rates listed in the Table. At steady state, measurements were made of systemic pressure, pulmonary artery pressure, and cardiac output. An inspection of the results from cases 2, 3, and 4 indicates that an infusion of PGI₂ has a dose related effect to increase cardiac output and decrease pulmonary and systemic arterial pressure and resistance. There was only a slight increase in heart rates.

Case 1 was ill and died 72 hours after the study. She was very sensitive to the hypotensive effect of PGI₂ and few data on cardiac output were obtained. Her pressure recordings, however, suggest similar haemodynamic responses to the other cases.

Discussion

The four cases presented here had classical signs of right ventricular strain on the electrocardiogram, and pulmonary hypertension with normal wedge pressures and no evidence of a major pulmonary embolus. None of them had completely normal respiratory function tests, but with the exception of case 4 these abnormalities were trivial. Cases 1 and 2 probably had true idiopathic pulmonary hypertension. Despite the normal pulmonary angiogram in case 3, the results of the lung scan and venogram strongly suggest that his pulmonary hypertension was on the basis of recurrent small pulmonary emboli. Case 4 had obstructive airways disease. Her blood gases, however, were within the normal range, and thus it is doubtful if parenchymal disease alone is the explanation for her pulmonary hypertension.

Our findings suggest that in these four patients whose pulmonary hypertension was presumably caused by pulmonary vascular disease, an infusion of PGI₂ decreased the pressure in the pulmonary artery and systemic circulation and increased the cardiac output. Similar changes have been reported in neonatal piglets with hypoxic pulmonary hypertension.¹⁶ Prostacyclin acts as a vasodilator¹⁷ and has no known positive inotropic action. Thus its beneficial effect on cardiac output is probably secondary to afterload reduction.

As indicated in the Table, the ratio of pulmonary to systemic vascular resistance in cases 1, 2, and 3 stayed constant or increased, suggesting that PGI₂ did not have a selective action on the pulmonary vasculature. It dilated the systemic vessels as well and in cases 1, 2, and 4 the infusion was curtailed because of symptomatic hypotension while the pulmonary artery pressure was still above the normal range. In advanced disease, however, there is severe pulmonary arteriolar fibrosis¹⁸ and thus the pulmonary vasculature may not be able to respond very much. It is interesting that in case 3 where the history was short and the aetiology presumably small pulmonary emboli, there was some selectivity and the pulmonary artery pressure dropped with no significant change in the systemic pressure. In this case, however, the patient became restless at an infusion rate of 8 ng/kg per min and this restlessness vanished within minutes of stopping the infusion. The only other significant side effects were nausea in all patients at an infusion rate above 8 ng/kg per min and widening of the QRS complex at an infusion rate of 16 ng/kg per min in one patient. From our limited experience it appears that prostacyclin is not therapeutically useful in pulmonary hypertension either of the primary variety or that secondary to lung disease or pulmonary emboli.

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