

Effects of prostaglandin E₁ on pulmonary circulation in patients with pulmonary hypertension

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SUMMARY The effects of prostaglandin E₁ on pulmonary circulation and left ventricular performance have been studied in 20 patients with mitral valve disease and pulmonary hypertension.

Prostaglandin E₁ was administered intravenously over a period of 30 minutes. The dose used was 0.01 µg/kg per min during the first 15 minutes and 0.02 µg/kg per min subsequently. The first dose led only to an insignificant fall in left ventricular end-diastolic pressure. Infusion of prostaglandin E₁ in a dose of 0.02 µg/kg per min resulted in a significant fall in the pulmonary arterial pressure ($P < 0.001$), total pulmonary resistance ($P < 0.001$), left ventricular end-diastolic pressure ($P < 0.001$), and aortic pressure ($P < 0.01$), and an increase in the pulmonary blood volume ($P < 0.01$), cardiac index ($P < 0.01$), and heart rate ($P < 0.05$). No significant differences were noted in stroke volume index or left ventricular dP/dt at 50 mmHg after prostaglandin E₁.

These results indicate that exogenously administered prostaglandin E₁ causes active vasodilatation of the pulmonary vascular bed and has no inotropic action on the cardiac muscle.

Though the effect of exogenously administered prostaglandin E (PGE) on the pulmonary circulation has been studied both in various species of animal and in healthy man (Bergström *et al.*, 1959, 1965; Hauge *et al.*, 1967; Carlson *et al.*, 1969; Hyman, 1969; Sobel and Robinson, 1969; Anderson *et al.*, 1971; Koss *et al.*, 1973; Kadowitz *et al.*, 1974), the part it plays in the regulation of the pulmonary circulation in disease has not yet been analysed. It has been assumed that PGE, which is liberated and metabolised in the lungs, fulfils the role of a local mediator influencing the pulmonary circulation in hypoxaemia or in anaphylactic reactions (Bergofsky, 1974).

The effect of exogenous PGE on the pulmonary vascular bed can be usefully studied in patients with mitral stenosis, in whom pulmonary vasoconstriction resulting from chronic hypoxaemia plays an important part in the development of pulmonary hypertension (Bergofsky, 1974).

Subjects and methods

The effect of prostaglandin E₁ (PGE₁) was studied in 20 patients, 4 men and 16 women, ranging

in age from 19 to 59 years (average 36.7 years). Mitral stenosis was present in all with mitral regurgitation also in 2 patients. The diagnosis was established by clinical examination and haemodynamic study, and was confirmed at operation in all cases. Heart failure was grade 2 and was found in 4 cases, grade 3 in 11, and grade 4 in 5, according to the NYHA classification. All the patients had pulmonary arterial hypertension: the mean value of the mean pulmonary arterial pressure was 38.5 ± 15.2 mmHg, and the total pulmonary resistance was 808.2 ± 387 dynes s cm⁻⁵ (10.1 ± 4.8 units). The majority of patients were receiving a digitalis preparation and a thiazide diuretic, but for 2 weeks before the investigation non-steroidal anti-inflammatory drugs were not given.

A prostaglandin solution was prepared immediately before the injection by dissolving PGE₁ (Upjohn Co. Ltd) in a 95 per cent ethanol solution. The appropriate dose of this solution was then diluted in 120 ml of 0.9 per cent saline. The preparation was administered by continuous intravenous infusion, using a Unipan peristaltic pump, in doses of 0.01 µg/kg per minute for 15 minutes and in doses of 0.02 µg/kg per minute for the subsequent 15 minutes. Informed consent was obtained from all patients.

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Table Effect of PGE₁ infusion on the haemodynamic indices studied in 20 patients with pulmonary hypertension

Patient no.	Age	Sex	Diagnosis and NYHA grade	Pulmonary artery mean pressure (mmHg)						
				Before PGE ₁	After PGE ₁			0.02 µg/kg per min		
					0.01 µg/kg per min 5'	10'	15'	5'	10'	15'
1	59	F	MS 3°	10.4	32	20.8	15.2	24	22.4	10.4
2	51	F	MS 2°	16	20	20	18	18	—	20.2
3	42	M	MS 3°	28.8	24	32	32	29.6	28	27
4	35	F	MS 3°	34.6	36	50	46	40	28	—
5	28	F	MS 3°	26.4	20	20.8	21.6	24	22.4	25.6
6	27	M	MS 3°	54	41.4	43.2	37.8	34.2	36.2	42
7	34	M	MS 3°	46	54	64	60	52	44	28
8	52	F	MS 3°	30.4	26.4	24.8	27	28.8	30.4	23.2
9	52	F	MS 2°	26.4	24	24	27.2	20	18.4	18.4
10	19	F	MS 4°	72	80	76	78	46	50	46
11	26	F	MS 3°	38	36	24	28	26	40	36
12	26	F	MS 2°	25.6	24	27.2	28	16.8	—	—
13	40	F	MS + MI 4°	50	48	48	48	44	40	38
14	20	F	MS + MI 4°	33.6	32.8	28	27.2	27.2	24	24
15	46	M	MS 4°	60	58	48	56	56	56	51
16	44	F	MS 3°	38	44	34	37	34	26	24
17	47	F	MS 3°	26.4	27.2	17.6	14.4	15.2	12	14
18	27	F	MS 3°	48	25	16	9.6	4	6.4	12
19	31	F	MS 4°	56	58	48	52	46	42	38
20	30	F	MS 3°	38	40	32	30	28	32	—
Mean value				38.05	37.7	34.9	34.6	32.6	31.0	28.8
Standard deviation				± 15.2	± 15	± 16.4	± 17.1	± 19.1	± 12	± 11.9
Significance of change					NS	NS	NS	*	†	‡

NS—not significant

* P < 0.05

† P < 0.01

‡ P < 0.001

The observations were made during right and left heart catheterisation, performed under local anaesthesia after premedication with 10 mg intramuscular diazepam. The following measurements were then made simultaneously: systolic, diastolic, and mean pulmonary artery pressures, left ventricular systolic and end-diastolic pressures, left ventricular dP/dt at 50 mmHg (Mason *et al.*, 1971), and heart rate, before and at 5-minute intervals during PGE₁ infusion. The pressure measurements were made using an EMT 35 pressure transducer, EMT 311 electromanometer amplifier, and Mingograf 81 recorder (Elema-Schönander), and left ventricular dP/dt with an EMT 63 differentiator. Cardiac output and pulmonary blood volume were measured initially and after 30 minutes of PGE₁ infusion by isotopic radiocardiography, using ¹³¹RIHA. The pulmonary mean transit time was calculated from the radiocardiograms as the difference between mean transit time of the right heart activity curve and the time of peak activity of the left heart curve (Donato *et al.*, 1962).

Pulmonary blood volume was calculated by multiplying mean transit time by stroke volume index. Total pulmonary resistance was calculated by the standard formula. Cardiac output, stroke volume, and pulmonary blood volume were ex-

pressed as indices by dividing by body weight (kg).

Changes in left ventricular function were assessed from (a) the LVEDP measurements from 10 consecutive cardiac cycles 0.05 s after the Q wave or at the peak of the R wave in the electrocardiogram; (b) the stroke volume and cardiac indices; (c) LV dP/dt at 50 mmHg. In addition, the aortic systolic, diastolic, and mean pressures were measured initially and after 30 minutes infusion of PGE₁. The results were analysed statistically, applying Student's t test for correlated variables.

Results

The haemodynamic changes during 30 minutes infusion of PGE₁ are given in the Table.

EFFECT OF PGE₁ ON PULMONARY CIRCULATION

During 15 minutes PGE₁ infusion in a dose of 0.01 µg/kg per minute had no significant effect on pulmonary arterial pressure. When the dose was increased to 0.02 µg/kg per minute, a fall in the pulmonary arterial systolic, diastolic, and mean pressures was already observed after 5 minutes, with a further drop at 10 and 15 minutes (Fig. 1). There was a significant drop in total pulmonary resistance

s cm ⁻⁵)	PBV (ml per kg)		LVEDP (mmHg)		LV dP/dt at 50 mmHg (mm/s)		CI (l/min per kg)		SVI (ml/beat per kg)		
	before PGE ₁	after PGE ₁	before PGE ₁	after PGE ₁	before PGE ₁	after PGE ₁	before PGE ₁	after PGE ₁	before PGE ₁	after PGE ₁	
349	10.8	9.24	12.4	9.0	2 032	2 293	0.052	0.064	0.53	0.58	
414	3.49	4.89	9.2	6.4	1 247	1 570	0.050	0.063	0.50	0.57	
827	4.95	3.92	8.4	4.0	693	693	0.040	0.033	0.38	0.35	
339	11.2	15.9	12.0	4.8	831	920	0.089	0.113	0.96	0.98	
426	6.89	8.63	8.8	6.0	785	1 120	0.061	0.084	0.76	0.76	
383	13.5	16.8	11.0	7.0	790	1 020	0.100	0.115	1.38	1.36	
514	11.0	11.6	4.8	1.6	831	1 110	0.082	0.086	0.91	1.02	
488	5.51	6.01	—	—	—	—	0.059	0.058	0.78	0.83	
313	10.1	10.8	4.0	2.8	1 155	1 020	0.090	0.088	1.13	1.10	
1 206	11.6	10.7	4.0	4.0	1 462	1 200	0.075	0.067	0.71	0.81	
—	—	—	5.2	3.2	—	—	—	—	—	—	
—	—	—	8.0	8.0	1 570	1 852	—	—	—	—	
399	8.61	11.7	4.0	1.6	1 108	1 108	0.059	0.087	0.70	0.67	
1 047	6.68	5.77	6.0	6.4	1 062	1 108	0.057	0.059	0.51	0.59	
—	—	—	13.2	9.2	1 016	1 180	—	—	—	—	
619	9.23	11.3	2.0	4.4	939	1 017	0.056	0.063	0.69	0.81	
236	11.1	12.5	10.0	3.6	842	890	0.069	0.076	1.12	1.17	
320	12.3	13.9	—	—	1 810	1 284	0.097	0.095	1.07	1.16	
809	9.68	12.5	9.2	5.0	1 057	1 117	0.063	0.073	0.76	0.61	
549	8.90	12.8	—	—	1 760	2 090	0.070	0.092	0.90	0.92	
2	544.6	8.77	9.63	7.78	4.94	1 138	1 198	0.068	0.077	0.81	0.84
	±273	3.30	4.49	±3.3	±2.3	±350	±428	0.017	0.022	0.28	0.28
	‡		†		‡		NS		†		NS

from 808.2 ± 387 dynes s cm⁻⁵ to 544 ± 273 dynes s cm⁻⁵ after 30 minutes infusion. The greatest decrease was observed in patients with initially high pulmonary resistances (Fig. 2). Pulmonary blood

volume rose from 8.77 ± 3.30 ml per kg to 9.63 ± 4.49 ml per kg after 30 minutes infusion. There was a slight and insignificant rise in pulmonary mean transit time.

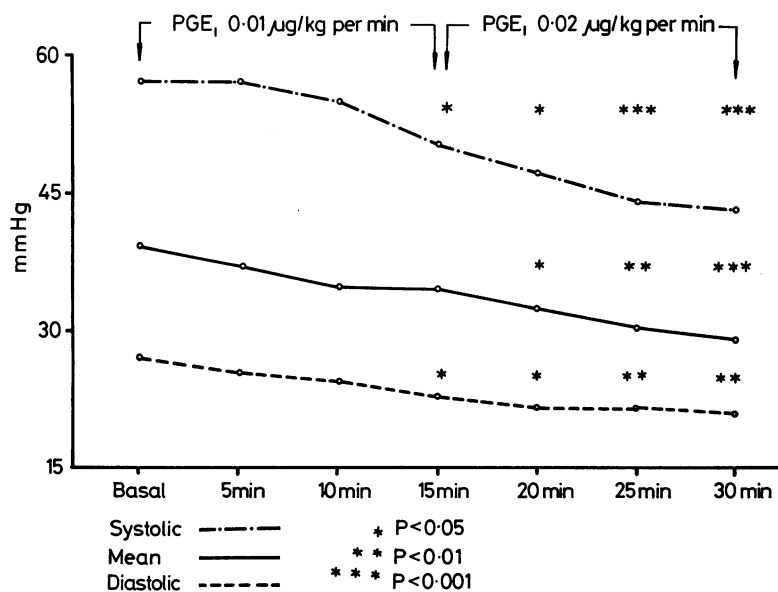


Fig. 1 Pulmonary arterial pressure after intravenous administration of PGE₁.

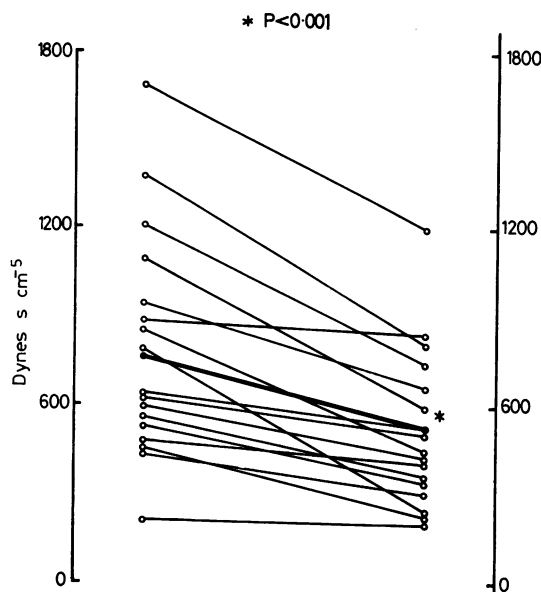


Fig. 2 The effect of PGE₁ on total pulmonary resistance. PGE₁ was administered intravenously in a dose of 0.01 µg/kg per minute for 15 minutes followed by a dose of 0.02 µg/kg per minute for the next 15 minutes.

EFFECT OF PGE₁ ON LEFT VENTRICULAR FUNCTION

PGE₁ in a dose of 0.01 µg/kg per minute lowered LVEDP even after 5 minutes infusion, with a further drop when the dose was increased to 0.02 µg/kg per minute. During 30 minutes of infusion the cardiac index rose significantly from 0.068 ± 0.017 l/min per kg to 0.077 ± 0.022 l/min per kg, and the heart rate also rose significantly from 87.2 ± 13 beats/min to 97.2 ± 17 beats/min ($P < 0.05$). At the same time the systolic, diastolic, and mean aortic pressures fell significantly ($P < 0.01$) and the total peripheral resistance fell by 25 per cent. Stroke volume index and LV dP/dt were unchanged by PGE₁ infusion.

SIDE EFFECTS

All patients showed flushing of the skin of the face and trunk within about 5 minutes of starting PGE₁ infusion in a dose of 0.02 µg/kg per minute, and 2 complained of epigastric pain and nausea. One patient developed a nodal rhythm with heart rate 40 beats/min between 15 and 20 minutes of starting PGE₁ infusion and 3 others developed sinus bradycardia with premature ventricular beats. These changes regressed spontaneously within 5 to 10 minutes of stopping PGE₁ administration. No patient had diarrhoea or fever.

Discussion

In patients with pulmonary hypertension accompanying mitral valve disease intravenous infusions of PGE₁ in doses of 0.01 to 0.02 µg/kg per minute caused a significant drop in pulmonary arterial pressure and total pulmonary resistance with a simultaneous increase in pulmonary blood volume. The fall in left ventricular end-diastolic pressure and rise of cardiac output in the absence of changes in stroke volume and left ventricular dP/dt does not necessarily mean that PGE₁ has a positive inotropic action on cardiac muscle. The fall in end-diastolic pressure may result from the fall in peripheral vascular resistance and a resulting decrease in venous return. The increased cardiac output can be attributed to increased heart rate.

The measurements of pulmonary blood volume and mean pulmonary artery pressure were made to determine the direction of the changes in the haemodynamics of the pulmonary circulation (Oakley *et al.*, 1962). In all those examined mean pulmonary artery pressure fell and pulmonary blood volume increased. This suggests an active dilatation of the pulmonary vascular bed during PGE₁ infusion (Fig. 3).

There have been no previous studies of the effects of PGE₁ on the pulmonary circulation in

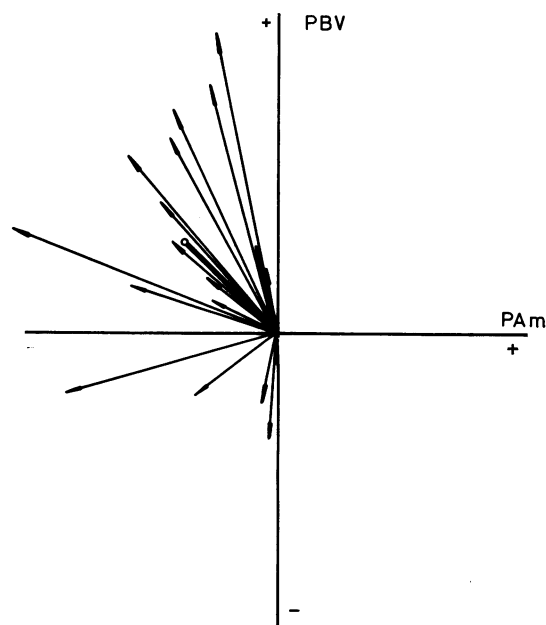


Fig. 3 Changes in pulmonary blood volume (Δ PVB) and pulmonary artery mean pressure (Δ PAm) after intravenous administration of PGE₁.

patients with vasoconstrictive pulmonary hypertension. Both Carlson *et al.* (1969) and Bergström *et al.* (1959) showed only a slight fall or no change in the pulmonary arterial pressure in subjects with normal pulmonary pressure and varying cardiac output. Joiner *et al.* (1975) observed dilatation of veins and slight constriction of the arterioles in isolated human pulmonary vessels under the influence of PGE₁. In experimental studies the effect of PGE₁ depended on the dose, the mode of administration, and the species of animal. Active vasodilatation of the pulmonary vascular bed was found in dogs, sheep (Kadowitz *et al.*, 1975), pigs (Kadowitz *et al.*, 1974), and rabbits (Hauge *et al.*, 1967). The studies of Nakano and McCurdy (1967) on dogs and of Koss *et al.* (1973) on cats showed no changes in the pulmonary circulation, however, while in calves Anderson *et al.* (1971) observed a rise in pulmonary pressure under the influence of PGE₁. Our studies on patients with vasoconstrictive hypertension showed active dilatation of the pulmonary vascular bed under the influence of PGE₁, as in the majority of animal species in experimental conditions.

Active dilatation of the pulmonary vascular bed has also been demonstrated under the influence of other substances stimulating adenylyl cyclase, for example isoprenaline (Schreiner *et al.*, 1968). The introduction of synthetic PGE₁ derivatives exhibiting a stronger biological action than PGE₁ itself, but without any harmful effects, may find an application in the lowering of pulmonary pressure in patients in whom pulmonary vasoconstriction is an important factor in their pulmonary hypertension.

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