Haemodynamic changes induced by prostacyclin in man

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SUMMARY Intra-arterial or intravenous infusion of prostacyclin at three dose levels (2, 5, and 10 ng/kg per min) in 10 subjects without evidence of coronary heart disease or cardiac failure, led to a distinct fall in peripheral and total pulmonary vascular resistances. This was accompanied by a drop in intra-arterial blood pressure, and the acceleration of heart rate. Stroke volume, cardiac output, mean right atrial pressure, and left ventricular end-diastolic pressure showed no significant changes. Except for sporadic headache no side effects occurred. Prostacyclin appears to act predominantly on resistance vessels. The haemodynamic effects produced by prostacyclin in man might be of clinical interest in the treatment of conditions associated with a significant rise in vascular resistance.

Prostacyclin (PGI$_2$) is a metabolite of arachidonic acid, generated by the arterial walls[1][2] and secreted into the circulation by the lungs.[3] In man, it blocks platelet aggregation, disperses circulating platelet aggregates, and causes vasodilatation.[4] It might well be that prostacyclin shields arteries against mural thrombosis and stops development of atherosclerosis.[5]

The remarkable properties of prostacyclin have been found beneficial in treating advanced arteriosclerosis obliterans.[6] They could also be useful in the management of atherosclerotic heart disease provided more was known about the haemodynamic effects of prostaglandin in man.

Patients and methods

The study included 10 men, aged 34 to 65 years, who underwent treatment with prostacyclin because of peripheral arterial disease. Arteriosclerosis obliterans was diagnosed in seven of them, and thrombangiitis in the remaining three. The diagnosis was based on typical history, clinical examination, and in each case it was confirmed by angiography. There was no evidence of either coronary heart disease or cardiac failure.

The patients had not received any drugs for a period of about a week preceding the infusion. The study was carried out in the intensive care unit under continuous electrocardiographic monitoring.

Cooled solution of lyophilised sodium salt of prostacyclin (synthesised by The Upjohn Com-

pany, Kalamazoo, Michigan, USA, and formulated by The Wellcome Research Laboratories, Beckenham, England) in glycine buffer pH 10·5 was infused during 72 hours. Six patients (cases 1, 2, 3, 7, 9, and 10) received infusions into the femoral artery of the affected limb, four others (cases 4, 5, 6, and 8) into the subclavian vein. The initial dose of 2 ng/kg per min was stepped up, first to 5 ng/kg per min and then to 10 ng/kg per min.

Right heart catheterisation was carried out with a 7F Swan-Ganz flow-directed thermodilution catheter, inserted through a cutdown in an ante-
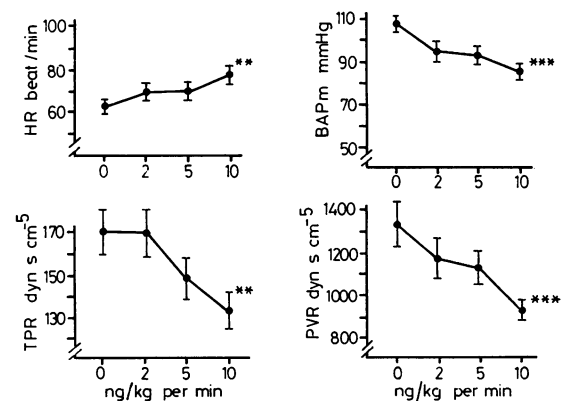

Fig. *The effects of prostacyclin infusion on heart rate (HR), mean brachial artery pressure (BAPm), total pulmonary resistance (TPR), and peripheral vascular resistance (PVR).*

Table 1 Changes in heart rate (HR), mean brachial artery pressure (BAPm), cardiac index (CI), stroke volume index (SVI), pulmonary end-diastolic pressure (PAEDP), and mean right atrial pressure (RAPm) after infusion of 5 and 10 ng/kg per min PGI_2

Case no.	Age (y)	HR (beat/min) PGI_2 (ng/kg per min) 0	5	10	BAPm (mmHg) PGI_2 (ng/kg per min) 0	5	10	CI (l/min per m²) PGI_2 (ng/kg per min) 0	5	10	SVI (ml/beat per m²) PGI_2 (ng/kg per min) 0	5	10	PAEDP (mmHg) PGI_2 (ng/kg per min) 0	5	10	RAPm (mmHg) PGI_2 (ng/kg per min) 0	5	10
1	59	78	98	93	130	124	92	3·18	2·79	3·66	40·8	28·5	39·5	11	8	10	0	—	1
2	48	58	70	73	105	100	71	3·06	3·35	3·03	52·8	47·8	37·9	7	6	8	2	—	3
3	49	58	77	88	120	100	100	2·66	3·65	3·80	45·9	47·4	40·0	7	4	9	2	1	4
4	70	56	57	72	130	110	100	3·20	3·24	4·09	55·2	57·9	73·1	10	8	4	3	2	3
5	48	61	73	85	100	90	90	3·25	3·57	4·07	52·7	48·6	47·6	12	10	13	6	0	4
6	47	44	56	66	110	90	90	3·52	3·75	4·85	80·0	67·1	73·5	12	14	8	6	8	8
7	50	71	58	59	95	74	75	4·90	4·16	4·10	68·8	70·5	70·6	11	8	8	3	3	3
8	64	73	76	86	100	80	77	3·03	3·18	3·45	41·2	41·8	38·4	8	9	8	2	5	-2
9	44	71	67	68	101	90	83	4·97	4·40	4·55	69·7	66·4	65·5	10	10	9	2	2	1
10	34	65	82	97	90	90	85	4·23	4·00	4·82	65·1	48·8	49·7	8	5	7	3	4	3
Mean ±SEM	51·9	63·5 ±3·1	71·4 ±4·1	78·7* ±4·0	108·1 ±4·4	94·8 ±4·5	86·3† ±3·1	3·6 ±0·2	3·6 ±0·1	4·0 ±0·1	57·2 ±4·1	52·4 ±4·1	53·5 ±4·8	9·7 ±0·6	8·2 ±0·9	8·3 ±0·7	2·8 ±0·6	2·7 ±0·8	2·7 ±0·8

*p < 0·02.   †p < 0·005.

Table 2 Changes in mean pulmonary artery pressure (PAm), pulmonary wedge resistance (PWR), total pulmonary resistance (TPR), peripheral vascular resistance (PVR), and left ventricular stroke work index (LVSWI) after infusion of 5 and 10 ng/kg per min PGI_2

Case no.	PAm (mmHg) PGI_2 (ng/kg per min) 0	5	10	PWR (dynes s cm⁻⁵) PGI_2 (ng/kg per min) 0	5	10	TPR (dynes s cm⁻⁵) PGI_2 (ng/kg per min) 0	5	10	PVR (dynes s cm⁻⁵) PGI_2 (ng/kg per min) 0	5	10	LVSWI (g m/m²) PGI_2 (ng/kg per min) 0	5	10
1	16	13	16	49·8	—	6·4	207	184	162	1621	1733	1000	66	45	38
2	11	13	12	92·0	98·1	62·2	161	168	173	1611	1416	1204	70	61	29
3	12	9	14	139·3	56·0	86·2	185	100	150	1858	1121	1077	67	58	49
4	16	8	12	140·8	52·9	31·4	241	158	83	1743	1455	1048	90	80	96
5	16	15	13	92·2	55·9	68·6	196	167	127	1229	1007	882	63	53	53
6	16	18	17	34·8	43·6	38·0	186	196	143	1279	981	760	106	126	77
7	15	13	12	61·1	84·0	48·7	153	156	146	968	888	913	78	63	64
8	10	11	10	109·8	143·4	138·4	137	144	129	1373	1046	932	51	40	36
9	15	14	13	59·1	85·0	75·5	126	132	112	853	850	781	86	72	65
10	11	9	13	48·1	56·0	63·3	105	86	101	866	916	718	72	56	52
Mean ±SEM	13·8 ±0·8	12·3 ±1·2	13·2 ±0·7	82·7 ±12	74·9 ±10·5	61·8 ±11·2	169·9 ±12·9	149·3 ±11·0	132·9* ±28·0	1340 ±115	1141 ±92	931† ±48	75·2 ±4·9	65·7 ±7·6	56† ±6·4

*p < 0·02.   †p < 0·005.

cubital vein. The catheter was connected to a 756 pressure transducer and 863 amplifier of Mingograf 82 recorder (Elema-Siemens) from which measurements of right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures were made. Cardiac output was measured using the thermodilution technique in triplicate, and the mean was calculated. Arterial blood pressure was determined continuously through a cannula inserted into the left brachial artery.

Cardiac output, stroke volume, and both left and right ventricular stroke work were expressed as indices by dividing by body surface. In calculating the left ventricular stroke work index pulmonary artery end-diastolic pressure was used instead of left ventricular end-diastolic pressure. Peripheral vascular resistance, total pulmonary resistance, and pulmonary wedge resistance were calculated by the standard formulae.

Simultaneously, external systolic time intervals were measured from the carotid artery and praecordial phonocardiogram and electrocardiogram. The differences between time intervals after correction for standard heart rate were compared.[7] Left ventricular dP/dt$_{max}$ was calculated by the indirect method[8] using the following formula for mean electromechanical $\Delta p/\Delta t$: BPd-PAEDP/PEP, where BPd is diastolic blood pressure in the brachial artery, PAEDP is pulmonary artery end-diastolic pressure, and PEP is pre-ejection period.

Additionally, in three of 10 patients both resting and hyperaemic calf muscle blood flows in the affected limbs were measured according to Lassen *et al.*, as described previously,[6] and expressed in ml per min per 100 g.

Student's t test for unpaired data was used in statistical evaluation.

Results

In all 10 patients the initial haemodynamic values studied were within the normal range, except for decreased resting and hyperaemic muscle blood flow. The changes in certain haemodynamic indices appeared early during infusion of the lowest dose of PGI$_2$. These changes became more pronounced with the increase in dose of the infused hormone. PGI$_2$ at a dose of 10 ng/kg per min caused a distinct fall in pulmonary vascular resistance from 1340 to 932 dynes s cm^{-5} ($p < 0.01$). At the same time arterial blood pressure (mean, systolic, and diastolic) fell on average by 20 per cent. Heart rate rose from mean 63/minute to 79/minute ($p < 0.01$), while left ventricular stroke work index declined from 75 to 56 g m/m^2 ($p < 0.05$). There was a mild, insignificant decrease

by 12 per cent in pulmonary wedge resistance. Total pulmonary resistance, however, fell significantly ($p < 0.05$) from mean 170 to 133 dynes s cm^{-5}. The following indices remained unaffected by the administration of PGI$_2$: cardiac output, cardiac index, stroke volume index, pulmonary artery end-diastolic pressure, and right atrial pressure. Mean electromechanical $\Delta p/\Delta t$ showed no changes during infusion of 2 and 5 ng/kg per min PGI$_2$, and fell during the administration of 10 ng/kg per min PGI$_2$. Systolic time intervals remained unchanged throughout PGI$_2$ infusion. Hyperaemic muscle blood flow increased in the affected limbs (from 3.3 ± 0.7 to 11.9 ± 3.0 ml/min per 100 g at 10 ng/kg per min PGI$_2$).

The route of administration of PGI$_2$ did not seem to affect the haemodynamic indices studied, which showed similar changes in patients receiving intra-arterial or intravenous infusions. In some patients prolonged infusion of high doses of PGI$_2$ caused headache or pain in the leg. Decrease in dose resulted in rapid disappearance of these symptoms. No other side effects occurred.

Discussion

Vasodilatory properties of PGI$_2$ described in man previously[9] explain several of the haemodynamic findings reported here. Of these, a pronounced fall in vascular resistance was the most striking phenomenon. This fall included pulmonary vascular resistance and total pulmonary resistance. It occurred even during infusion of the lowest dose of PGI$_2$, progressed in a dose-dependent manner, and was accompanied by a distinct rise in muscle blood flow. These effects were most striking in the subjects with basic pulmonary vascular resistance values close to the upper limit of the normal range. Thus, in four patients with basic values between 1500 to 1800 dynes s cm^{-5} pulmonary vascular resistance fell on average by 40 per cent, while in the remaining six patients (basic values below 1500 dynes s cm^{-5}) it declined by only 24 per cent.

A similar dose-dependent fall in pulmonary vascular resistance after PGI$_2$ injection was reported recently in several experimental animal models.[10] [11] Man, however, appears to be more sensitive to PGI$_2$ than the animals studied. Infusion of five to 10 times lower concentrations of prostacyclin to man than to the animals[10] [12] [13] resulted in a similar fall in pulmonary vascular resistance in both groups.

In comparison to prostaglandin E$_1$ (PGE$_1$) prostacyclin has a stronger vasodilatatory action in man. Doses of PGE$_1$[14] at least twice as high were necessary to reduce pulmonary vascular resistance to the range similar to that reported here. Prostacy-

clin was also better tolerated than PGE₁. We have not observed abdominal cramps or back pain, which were frequently recorded in subjects receiving PGE₁, and which had necessitated interruption of the infusion.[15]

Although PGI₂ depressed significantly total pulmonary resistance, its effects on the pulmonary bed were less pronounced than those on peripheral vascular resistance. Thus, during the administration of PGI₂ at a dose of 10 ng/kg per min pulmonary wedge resistance fell by 12·5 per cent, total pulmonary resistance by 21·7 per cent, and peripheral vascular resistance by 30·4 per cent—in comparison with initial values. Similarly, Kadowitz et al.[16] obtained a more pronounced fall in systemic than pulmonary vascular resistance in dogs receiving PGI₂. Though neither in animals nor in men were these differences of striking magnitude, they nevertheless might suggest that the two vascular beds vary in sensitivity to PGI₂. This observation seems interesting, since the sensitivity to the vasodilatating action of prostaglandins varies between the different vascular regions, being highest in the skeletal muscle vasculature and lowest in the splanchnic vascular bed. Moreover, in the skeletal muscle vascular bed, the PGI₂ synthetic pathway is quantitatively the most important.[17]

The falling vascular resistance caused a drop in arterial blood pressure, reaching the level of significance at a dose 10 ng/kg per min. The acceleration of heart rate, which followed, could be looked upon as an autoregulatory mechanism, triggered by a fall in blood pressure. This acceleration together with a slight fall in stroke volume index resulted in the small increase in cardiac index, which did not reach the level of statistical significance. Left ventricular stroke work index decreased significantly during infusion of 10 ng/kg per min PGI₂. Lower doses of PGI₂ (2 and 5 ng/kg per min), which did not reduce afterload, however, caused no changes in either left ventricular stroke work index or cardiac index, left ventricular $\Delta p/\Delta t$, and systolic time interval. It appears, therefore, that PGI₂ in the above doses has no direct inotropic effects.

Our overall impression is that prostacyclin acts predominantly on the resistance vessels. This suggestion stems from the following haemodynamic changes occurring during PGI₂ infusion: (1) fall in vascular resistance; (2) increase in muscle blood flow; (3) lack of changes in mean right atrial pressure. Prostacyclin, therefore, could be valuable not only in the treatment of peripheral arterial disease,[6][18] but also in clinical conditions associated with significant rise in vascular resistance, including pulmonary hypertension, hypertensive emergencies,

and cardiogenic shock. Clinical studies with prostacyclin seem warranted in heart failure, a condition affected favourably by vasodilators through lowering of afterload and subsequent improvement of failing left ventricle.[19][20] If prostacyclin, indeed, finds application in the above clinical situations, then it might be advantageous in comparison with the currently used vasodilators, since its potentially useful haemodynamic effects occur even at low doses (2 to 10 ng/kg per min) which cause no serious side effects.

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