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Prostacyclin-induced changes in coronary blood flow and oxygen handling in the normal and acutely ischaemic canine myocardium

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Introduction

Prostacyclin, a metabolite of arachidonic acid, which is synthesized mainly by vascular tissue (1), causes hypotension in anaesthetized dogs (3). Direct intra-coronary injection of prostacyclin has been shown to increase coronary blood flow (2). Prostacyclin has also been shown to exert a protective effect during acute myocardial ischaemia in cats (9) and to reduce mortality following coronary artery ligation in conscious dogs (5). There is one report (10) that prostacyclin reduced blood flow in the normal canine myocardium without altering flow in the ischaemic myocardium and another (4) in which prostacyclin reduced blood flow in the ischaemic region but did not change flow in the normal myocardium. In view of these conflicting results we have investigated the effects of prostacyclin on coronary blood flow, vascular resistance and oxygen utilisation in both the normal and the acutely ischaemic myocardium. The effect of prostacyclin on the electrocardiographic consequences of short coronary artery occlusions was also studied.

Methods

The studies were carried out in greyhounds anaesthetized with chloralose and maintained on positive pressure ventilation with 100 % oxygen. A left thoracotomy was performed, the heart suspended in a pericardial cradle, and the left anterior descending coronary artery (LAD) was ligated. After the cessation of cardiac arrhythmias (30 minutes after ligation) the distal portion of the LAD was cannulated to allow the recording of peripheral coronary pressure (PCP). Blood flow in the ischaemic area was assessed using a xenon clearance technique (8), and flow in the essentially normal myocardium was measured with an electromagnetic flow probe placed around the left circumflex coronary artery. A local coronary vein draining the ischaemic area was catheterized using the Seldinger technique, and blood from the normal myocardium was obtained from a fluoriscopically positioned coronary sinus catheter. Blood samples were analysed for PO_2, PCO_2, pH and haemoglobin (6).

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Table 1. The effect of intravenously administered prostacyclin on pressure, flow, oxygen consumption and vascular resistance in the essentially normal and the acutely ischaemic myocardium. Each value is the mean ± s.e.m. (n = 5 to 14); * indicates a statistically significant difference from control, dependent t-test, $P < 0.05$.

	normal myocardium				ischaemic myocardium			
	mean BP (mm Hg)	coronary flow (ml/min)	O_2 consumption (ml/min)	vascular resistance	mean PCP (mm Hg)	infarct flow (ml 100 g^{-1} min^{-1})	O_2 consumption (ml 100 g^{-1} min^{-1})	vascular resistance
Control	126 ± 6	37 ± 7	5.73 ± 0.70	4.16 ± 0.89	28 ± 3	19 ± 2	3.40 ± 0.62	1.57 ± 0.14
Prostacyclin 0.1 µg kg^{-1} min^{-1}	108 ± 9*	42 ± 10	5.67 ± 0.79	2.99 ± 0.69	26 ± 3	14 ± 3*	2.38 ± 0.44	2.15 ± 0.30
Control	114 ± 8	60 ± 12	9.05 ± 1.79	2.37 ± 0.45	34 ± 3	9 ± 3	3.26 ± 0.30	1.89 ± 0.16
Prostacyclin 0.5 µg kg^{-1} min^{-1}	69 ± 9*	42 ± 13	4.97 ± 1.13*	1.97 ± 0.56	19 ± 2*	9 ± 1*	1.60 ± 0.23*	2.52 ± 0.46

In some animals, which were subject to short (3 minute) occlusions of the LAD, electrocardiograms (ECGs) were recorded from nine epicardial electrodes which were embedded in a rubber pad sutured to the myocardium (7). Prostacyclin, in 10 % ethanol in saline, was administered as an infusion either intravenously, or directly into the ischaemic myocardium via a cannula placed alongside the cannula used to record PCP. The effects of prostacyclin were measured after 5 minutes of infusion.

Results

The administration of prostacyclin (0.01 to 1 μg kg^{-1} min^{-1}) by intravenous infusion caused dose dependent decreases in arterial blood pressure and PCP but did not significantly alter heart rate, pulmonary artery pressure or LV dP/dt. At a dose of 0.1 μg kg^{-1} min^{-1} prostacyclin reduced blood flow and oxygen consumption in the ischaemic myocardium but did not alter these parameters in the normal myocardium. A higher infusion rate, 0.5 μg kg^{-1} min^{-1} resulted in decreases in blood flow and oxygen consumption in both the ischaemic and the normal myocardium (table 1). There was a significant correlation between infarct blood flow and peripheral coronary pressure (fig. 1). Since changes in PCP reflect changes in arterial pressure, this suggests that the reduction in blood flow in the ischaemic myocardium resulted from the ability of prostacyclin to cause systemic vasodilatation.

In order to eliminate the influence of systemic hypotension, prostacyclin (0.005 μg kg^{-1} min^{-1}) was infused directly into the ischaemic myocardium. This resulted in reductions in infarct blood flow and oxygen consumption (fig. 2). As with intravenous administration, the reduction in oxygen consumption resulted directly from reduced oxygen availability.

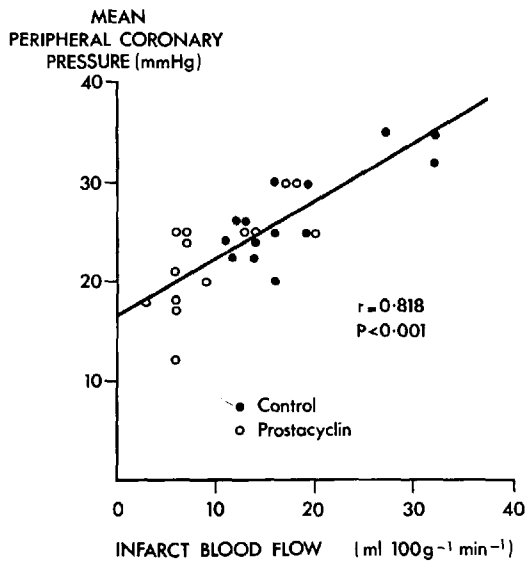

Fig. 1. Correlation between peripheral coronary pressure (PCP) and infarct blood flow before and after the intravenous administration of prostacyclin.

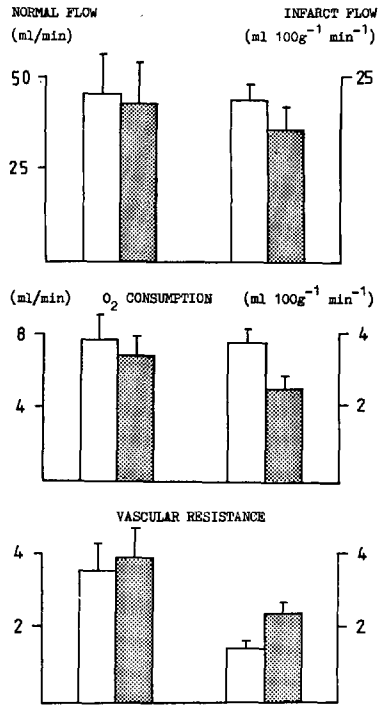

Fig. 2. The effects of locally administered prostacyclin (shaded columns) on blood flow, oxygen consumption and vascular resistance in the essentially normal and in the acutely ischaemic myocardium (Mean ± s.e.m., n = 5).

There was no change in the amount of oxygen extracted during passage across the myocardium. Vascular resistance tended to increase in the ischaemic myocardium and to decrease in the normal myocardium during both local and intravenous administration of prostacyclin. This may indicate that prostacyclin has different effects in the normal and the ischaemic regions.

Short occlusions of the LAD resulted in marked elevation of the ST-segment measured from epicardial electrodes overlying the area rendered ischaemic by occlusion. Prostacyclin (0.5 μg kg^{-1} min^{-1}) reduced the change in ST-segment elevation resulting from 3-minute coronary artery occlusions (fig. 3). This reduction in ST-segment elevation occurred with a dose of prostacyclin which markedly reduced arterial pressure.

Discussion

Prostacyclin, administered either locally or intravenously, reduced blood flow in the ischaemic myocardium and increased vascular resistance in this region. In the normal myocardium, however, vascular resistance tended to decrease with prostacyclin and, at the lower infusion rate, blood flow tended to increase. This suggests that there may have been

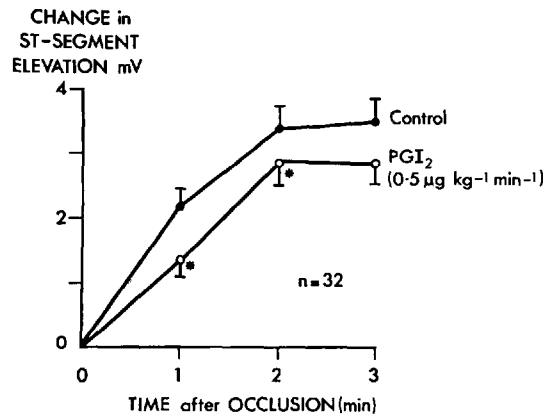

Fig. 3. The effect of prostacyclin on the change in ST-segment elevation 1, 2 and 3 minutes after coronary artery occlusion. Each point represents the mean ± s.e.m. of the change in ST-segment elevation in individual electrodes in 5 animals.

some degree of vasodilatation in the normal myocardium but that this was masked by the concomitant reduction in arterial pressure. If prostacyclin increased blood flow in the normal region, this could result in blood being diverted away from the ischaemic myocardium – a 'coronary steal' effect. This would explain the observed reductions in infarct blood flow following prostacyclin administration.

These studies demonstrate two effects of prostacyclin that are consistent with the finding (9) that it may exert a protective effect during myocardial ischaemia. Firstly, prostacyclin consistently reduced oxygen consumption in the ischaemic area, an effect that paralleled the decreased nutritive blood flow. Secondly, it reduced ST-segment elevation resulting from short (3 minute) coronary artery occlusions (fig. 3) despite a reduced coronary perfusion pressure (table 1). The mechanism of these effects is at present unknown.

Key words: prostacyclin, coronary flow, ischaemic myocardium, oxygen utilization

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ERRATUM

T. Takala. **Protein synthesis in the isolated perfused rat heart. Effects of mechanical work load, diastolic ventricular pressure and coronary pressure on amino acid incorporation and its transmural distribution into left ventricular protein.** Basic Res. Cardiol. **76,** 44–61 (1981). The last three lines in the legend of Table 1 on page 50 should read:
oxygen consumption at time 60 min are shown. P (versus group II) *) < 0.05, **) < 0.02, ***) < 0.001, P (versus group VI), ^{2}) < 0.05, ^{3}) < 0.01.

Für die Schriftleitung verantwortlich: Prof. Dr. R. Jacob, Physiologisches Institut II, Gmelinstraße 5, D-7400 Tübingen, und Prof. Dr. W. Schaper, Institut für experimentelle Kardiologie im William-G.-Kerckhoff-Institut, Benekestraße 2, D-6350 Bad Nauheim. – Anzeigenverwaltung: Springer-Verlag GmbH & Co. KG, Kurfürstendamm 237, D-1000 Berlin 15 – Verantwortlich für den Anzeigenteil: E. Lückermann. – Verlag: Dr. Dietrich Steinkopff Verlag, Saalbaustraße 12, Postfach 11 10 08, D-6100 Darmstadt 11. – Satz und Druck: Ungeheuer + Ulmer KG GmbH + Co, Körnerstraße 14–18, Postfach 10 40, D-7140 Ludwigsburg.