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THE ACTION OF NITROGLYCERINE AND DIPYRIDAMOLE IN NORMAL AND ISCHAEMIC DOG HEART

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1 Network and post-network resistances were measured together with heat clearance and heat production in the myocardium.

2 Nitroglycerine dilated all resistance vessels but was twice as effective on network as compared with post-network vessels.

3 Dipyridamole dilated network and post-network vessels equally.

4 Nitroglycerine had no effect on heat clearance or heat production in ischaemic myocardium.

5 Dipyridamole increased heat clearance in normal but not in ischaemic myocardium.

6 Dipyridamole depressed heat production in normal and ischaemic myocardium.

7 That the clinical effectiveness of nitroglycerine does not depend entirely on its coronary vasodilator properties is confirmed.

8 It is suggested that the action of dipyridamole in depressing myocardial heat production may be due to an action on the efficiency of oxygen utilization during cardiac contraction.

Introduction

How vasodilator agents relieve angina is still not understood. Nitroglycerine and dipyridamole offer a nearly classic paradox underlining the problem. Nitroglycerine, although only a moderate coronary vasodilator, remains the most effective clinical preparation in the treatment of angina. Dipyridamole, a much more powerful coronary vasodilator, is relatively ineffective.

According to Fam & McGregor (1968) nitroglycerine has a prolonged vasodilator action on large conducting coronary arteries but little action on the microcirculation. The ischaemic process itself was thought to bring about local vasodilatation of the microvessels. These workers also showed that dipyridamole had little action on the conducting arteries but was markedly vasodilator to the microcirculation. Assuming the vessels of an ischaemic region to be already fully dilated by hypoxia, dipyridamole can only dilate vessels of the surrounding unaffected myocardium. With no change in calibre of the conducting arteries Fam & McGregor deduced that flow in the ischaemic area 'would be unaffected or even reduced' by dipyridamole. Later the 'steal' phenomon was more specifically invoked; it was concluded that dilatation of vessels surrounding an ischaemic area would reduce perfusion pressure so that the ischaemic area, with its widely dilated blood vessels, would in fact suffer a reduction in blood flow (Rowe, 1970).

There has been recent evidence, however, throwing doubt on the assumption that following acute artery ligation blood vessels in the developing infarct are fully dilated. Indeed there is good evidence of precapillary closure (Grayson, 1973). This would cast doubt on the 'steal' phenomenon as a factor in the clinical ineffectiveness of dipyridamole. Thus there is a clear necessity to re-examine the haemodynamic consequences of acute artery ligation and the actions of both nitroglycerine and dipyridamole on coronary vascular resistance, local tissue blood flow, and heat production in the normal and ischaemic heart.

Methods

Twenty mongrel dogs of either sex, 10 to 16 kg in weight, were anaesthetized with an intravenous injection of sodium pentobarbitone (30 mg/kg). Aortic pressure was measured by means of a cannula positioned in the arch of the aorta via the left common carotid artery and connected to a Statham strain gauge (model P23H). Central venous pressure was measured from a cannula

positioned in the right atrium via the right external jugular vein and connected to a Statham strain gauge (model P23AA). Intraventricular pressure was measured with a cannula inserted in the left ventricle through the aortic valves, and connected to a Statham strain gauge (model P23AA). A femoral artery for arterial blood sampling, and a femoral vein for intravenous infusions were also cannulated. Positive pressure ventilation was maintained through a tracheal cannula by means of a Harvard respirator, using a mixture of room air and 95% O_2 and 5% CO_2. The air intake was bubbled through a flask of heated water so that saturated air at an appropriate temperature was delivered to the dog. Arterial blood samples were taken at 15 min intervals throughout the experiment, and arterial pH, PO_2 and PCO_2 were evaluated with a Radiometer Blood Micro System (Type BMS 3). Arterial PO_2 was maintained at 100 mmHg by adjusting the richness of the inhalation mixture, and PCO_2 at 40 mmHg by adjusting the respiration rate. Rectal temperature was monitored with an Elektrolaboratoriet electric universal thermometer (Type T3). Electrocardiogram readings from standard lead II were constantly monitored.

A thoracotomy was performed through the fifth left intercostal space, the pericardium was incised, and the heart suspended in a pericardial cradle. The left anterior descending coronary artery was dissected free as near the origin as possible, and fitted with an electromagnetic flowmeter probe (Zapeda). A snare was placed around the artery distal to the flowmeter probe to obtain zero flow for the calibration of the flowmeter. The anterior descending coronary artery was also dissected free just proximal to the last bifurcation and a ligature placed loosely around it for the purpose of subsequent ligation. Two heated thermocouple probes were used for the assessment of the apparent myocardial thermal conductivity increment over non-perfused tissue (which is directly proportional to local tissue blood flow), and heat production by means of a heat clearance technique (Grayson, Coulson & Winchester, 1971). One probe was implanted in the tissue immediately distal to the occluding ligature, and the other in the tissue proximal to the ligature.

The chest was closed with clamps, and a period of 30 min was allowed for a steady state to be attained. Control measurements were then carried out. Data were recorded continuously on a Varian Statos III electrostatic recorder.

Ten dogs then received an intravenous infusion of nitroglycerine (0.6 mg dissolved in 10 ml isotonic saline) infused over a period of one minute. Ten dogs received a similar infusion of dipyridamole (0.5 mg/kg in 10 ml saline). Data were recorded continuously after administration of either drug until haemodynamic indices returned to control values (usually withon 10 to 12 min for nitroglycerin, and 20 to 25 min for dipyridamole).

The chest was reopened and the distal portion of the anterior descending coronary artery was ligated and cannulated distally for the measurement of peripheral coronary pressure (p.c.p.). The chest was then closed in layers, and a period of 30 min allowed for the achievement of a steady state. An infusion of either nitroglycerine or dipyridamole was then administered hourly for 6 h beginning 1 h after ligation.

Data obtained immediately before the administration of either drug provided control values. Control values for each index represent the mean of a 6-7 min period.

Myocardial vascular resistance was calculated as the ratio of effective perfusion pressure and flow and was calculated for both systole and diastole using peak systolic and end-diastolic parameters. Total coronary vascular resistance was calculated as follows:

$$\frac{\text{aortic pressure} - \text{central venous pressure}}{\text{anterior descending flow}},$$

Total resistance was further partitioned into two components, network resistance and post-network resistance using peripheral coronary pressure. Network resistance was calculated as follows:

$$\frac{\text{aortic pressure} - \text{p.c.p.}}{\text{anterior descending flow}}$$

and represents resistance to flow in vessels of the network, including the large conducting arteries. Post-network resistance was calculated as the difference between total and network resistance, and probably represents the resistance of small arterioles, precapillaries and capillaries. The statistical significance of the data was determined by the paired *t*-test.

Results

The effect of vasodilator stimuli before and after occlusion of the anterior descending coronary artery

Nitroglycerine. Figure 1 is a record of haemodynamic events from a typical experiment. In the doses used in these experiments, nitroglycerine reduced both systolic and diastolic aortic pressures. Blood flow in the anterior descending coronary artery initially rose both in diastole and in systole. The systolic rise, however, was maximal

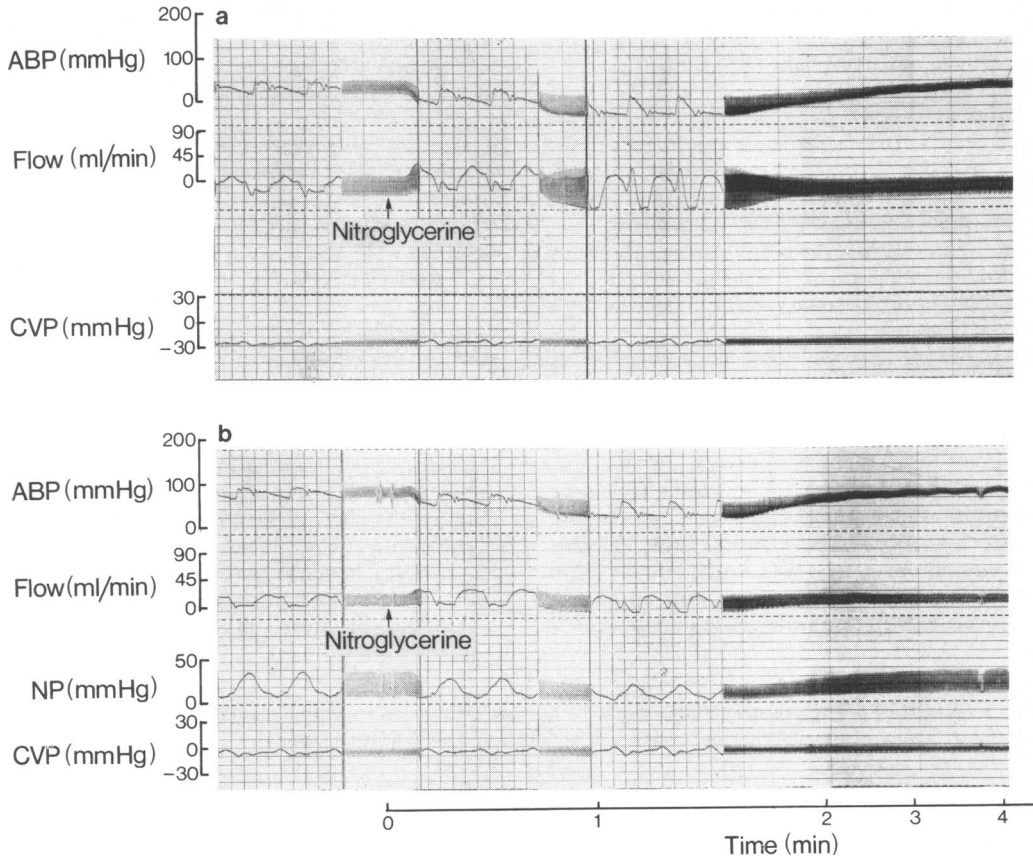

Figure 1 Effect of nitroglycerine on arterial blood pressure (ABP), anterior descending coronary blood flow, central venous pressure (CVP) and peripheral coronary pressure (NP) before and after ligation of the anterior descending coronary artery.

in 15 s and systolic flow began to fall either at the same time as the beginning of the systemic blood pressure drop or shortly after. Diastolic flow continued to rise to maximum levels usually seen at about 20 seconds. Systolic flow fell in most experiments to levels below the preinjection control values. In many experiments it fell briefly to zero and in some experiments as in Figure 1 (those in which the arterial blood pressure fell very markedly), brief periods of backflow were recorded. The total effects were short-lived and usually over within 2 min of the injection.

The effect of nitroglycerine on total resistance before artery ligation, 1 h post-ligation, and 6 h post-ligation is shown in Table 1. Although resistance was increased following ligation, the pattern of change following nitroglycerine administration was not altered. Thus in diastole, resistance at all times, even 6 h after ligation, fell by nearly 30% within 15 s and reached minimum levels of 46% below control levels in 60 seconds. In systole the pattern was different; 15 s after injection (before aortic pressure had fallen) there was a drop of about 30% in resistance but this was not sustained. In some cases there followed brief periods of increased resistance and even zero flow was recorded in some experiments. However, the secondary systolic rise in total resistance was very variable, and in the whole series was not statistically significant.

Table 2 gives the results obtained 1 h post-ligation in terms of network and post-network resistances. At 15 s there was a decline in both network and post-network resistance, similar in systole and diastole. The decline was significant in all cases ($P < 0.05$). At 60 s, the effect of nitroglycerine in diastole was twice as great on network vessels as on post-network vessels. In

systole, the effect on resistance was the same in network and post-network vessels, namely an increase which was significant ($P < 0.001$).

Dipyridamole Figure 2 is a record of haemodynamic events from a typical experiment. There was a slow fall in systemic arterial pressure, relatively minor in systole (16 mmHg) but with a more pronounced fall in diastole (32 mmHg).

There was a slowly developing but ultimately very marked increase in diastolic flow in the anterior descending coronary artery, systolic flow showing little change.

After ligation, the picture was essentially the same. The aortic pressure responses were unaltered. Network pressure fell by about 3 mmHg in systole and about 5 mmHg in diastole.

Calculated resistances are shown in Table 1. The proportionate changes in resistance following dipyridamole were much the same as before ligation both at 1 h and at 6 hours. Table 2 shows that the maximum effect was much the same on post-network as on network vessels both in systole and in dimstole. Dipyridamole caused about a 50% decline in total resistance with an effect on the network vessels which is greater in diastole than in systole. Its effect on post-network vessels was not significantly greater in diastole.

Effect of nitroglycerine and dipyridamole on myocardial heat production

Figure 3 shows the effect of nitroglycerine and dipyridamole on myocardial heat production expressed as I^2 equivalents.

Nitroglycerine Heat production was not significantly altered by nitroglycerine in either the proximal or the distal myocardium, before or after artery ligation (Figure 3a).

Dipyridamole Myocardial heat production was considerably depressed by dipyridamole (Figure 3b). Before ligation, in both areas of the myocardium, the decline was rapid, minimum levels being reached within 2 minutes. This was followed by a gradual return to control levels.

In the proximal myocardium, dipyridamole

Table 1 Effect of nitroglycerine and dipyridamole on total systolic and diastolic resistance to flow in the territory of supply of the anterior descending artery before and after acute ligation.

		Nitroglycerine (n = 10)			*Dipyridamole* (n = 6)	
		Control	*15 s*	*60 s*	*Control*	*max. effect*
Pre-ligation	systole	3.57 ± 0.53	2.86 ± 0.32	3.97 ± 0.64	6.65 ± 1.51	3.02 ± 0.73
	diastole	1.84 ± 0.24	1.10 ± 0.12	1.02 ± 0.10	2.43 ± 0.51	1.15 ± 0.36
1 h post-ligation	systole	6.00 ± 1.40	4.60 ± 1.10	9.60 ± 3.40	6.40 ± 1.95	2.76 ± 0.64
	diastole	3.30 ± 0.70	2.30 ± 0.50	1.90 ± 0.40	2.11 ± 0.59	0.76 ± 0.19
6 h post-ligation	systole	4.90 ± 1.13	4.00 ± 1.10	4.80 ± 1.50	5.90 ± 1.76	2.90 ± 0.70
	diastole	2.40 ± 0.60	1.70 ± 0.50	1.10 ± 0.20	2.37 ± 0.60	1.20 ± 0.30

Resistance is expressed in peripheral resistance units.
Values are mean ± s.e. mean.

Table 2 The effect of nitroglycerine and dipyridamole on network and post-network resistances one hour after ligation.

		Network		*Post-Network*	
		Systolic	*Diastolic*	*Systolic*	*Diastolic*
Nitroglycerine	15 s	−20.1 ± 3.4*	−28.6 ± 5.3*	−28.0 ± 8.1*	−22.2 ± 5.4*
(*n* = 10)	60 s	+36.5 ± 20.8**	−46.1 ± 5.4	+37.8 ± 2.4**	−22.0 ± 5.0
Dipyridamole (*n* = 6)		−40.7 ± 8.6**	−60.7 ± 7.8**	−48.9 ± 9.4**	−55.0 ± 8.2**

Results are expressed as % change. Nitroglycerine = 0.6 mg; dipyridamole = 0.5 mg/kg.
With nitroglycerine at 60 s, the diastolic decline in network resistance was significantly greater than diastolic decline in post-network resistance ($P < 0.001$). With dipyridamole, network decline in diastolic resistance was significantly greater than decline in systolic resistance ($P < 0.05$).
Values are mean ± s.e. mean. *$P < 0.05$; **$P < 0.001$.

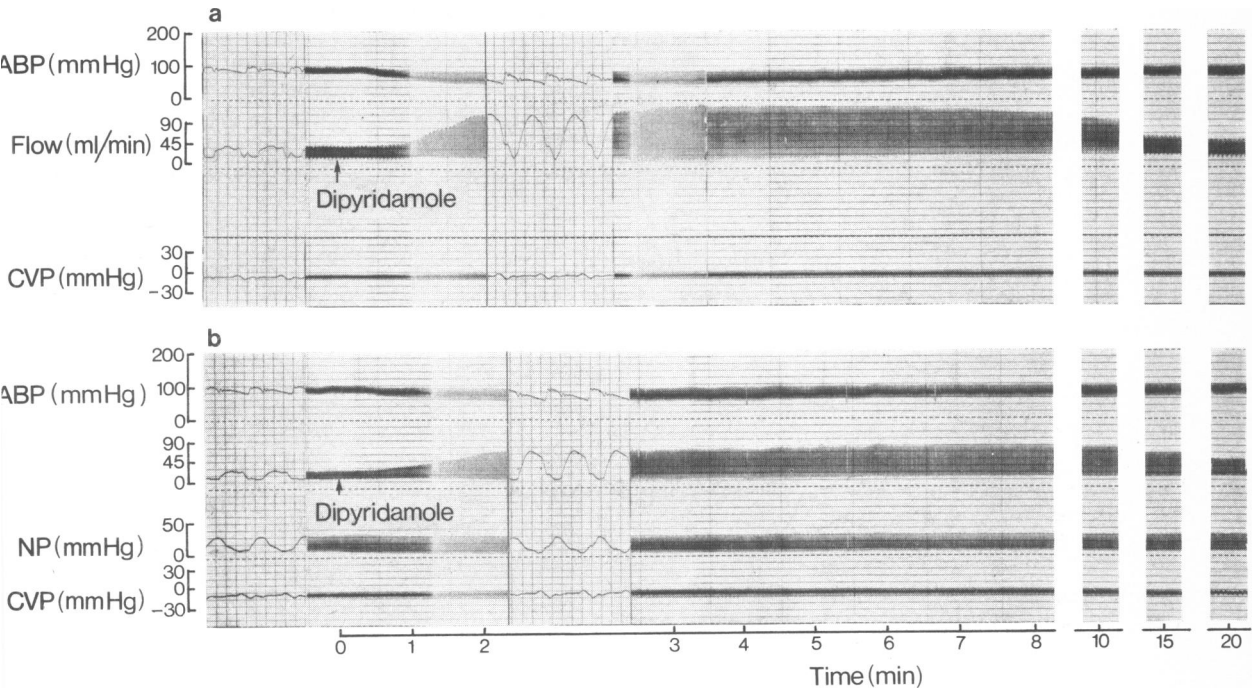

Figure 2 The effect of dipyridamole on arterial pressure (ABP), flow in the anterior descending coronary artery, central venous pressure (CVP) before ligation and its effect on the same parameters together with peripheral coronary pressure (NP), post-ligation.

produced similar declines in heat production throughout the experiment. The decline in heat production before ligation was 65% ($P < 0.05$). At 1 h and at 6 h post-ligation the declines were 69% ($P < 0.01$) and 41% ($P < 0.01$) respectively.

However, in the distal myocardium the effect of dipyridamole was altered after ligation. Before ligation, dipyridamole produced a decline in heat production of 54% ($P < 0.01$). One hour following ligation, the control level of heat production in the ischaemic muscle was depressed, showing some recovery by 6 hours. In spite of the fact that initial levels of heat production were lower following ligation dipyridamole still produced a further decline in heat production, although the magnitude of the response was reduced. Thus 1 h post-ligation the fall in heat production produced by dipyridamole was 39% ($P < 0.05$), and at 6 h the fall was 32% ($P < 0.05$).

The effect of nitroglycerine and dipyridamole on myocardial thermal conductivity increment (Δk).

Figure 4 shows the effect of nitroglycerine and dipyridamole on heat clearance (thermal conductivity increment) expressed in thermal conductivity units.

Nitroglycerine In the proximal myocardium, before ligation, the initial slight rise and subsequent decline in flow following the administration of nitroglycerine (Figure 4a) were not statistically significant. However, at 1 h and at 6 h the flow declines of 27% and 19% respectively were significant ($P < 0.05$).

In the distal myocardium, before ligation, nitroglycerine injection caused a significant decline in flow of 30% ($P < 0.05$). One hour post-ligation the fall was 38% ($P < 0.05$). Six hours post-ligation the decline in flow was not significant.

Dipyridamole Before ligation, dipyridamole had marked effects on local blood flow in both the proximal and the distal myocardium (Figure 4b). Flow increased, reaching maximal levels in about 4 min, thereafter declining gradually toward control values.

In the proximal myocardium, before ligation, dipyridamole increased Δk by 134% ($P < 0.05$). Post-ligation the dilator effect was sustained. At 1 h dipyridamole increased flow by 95%

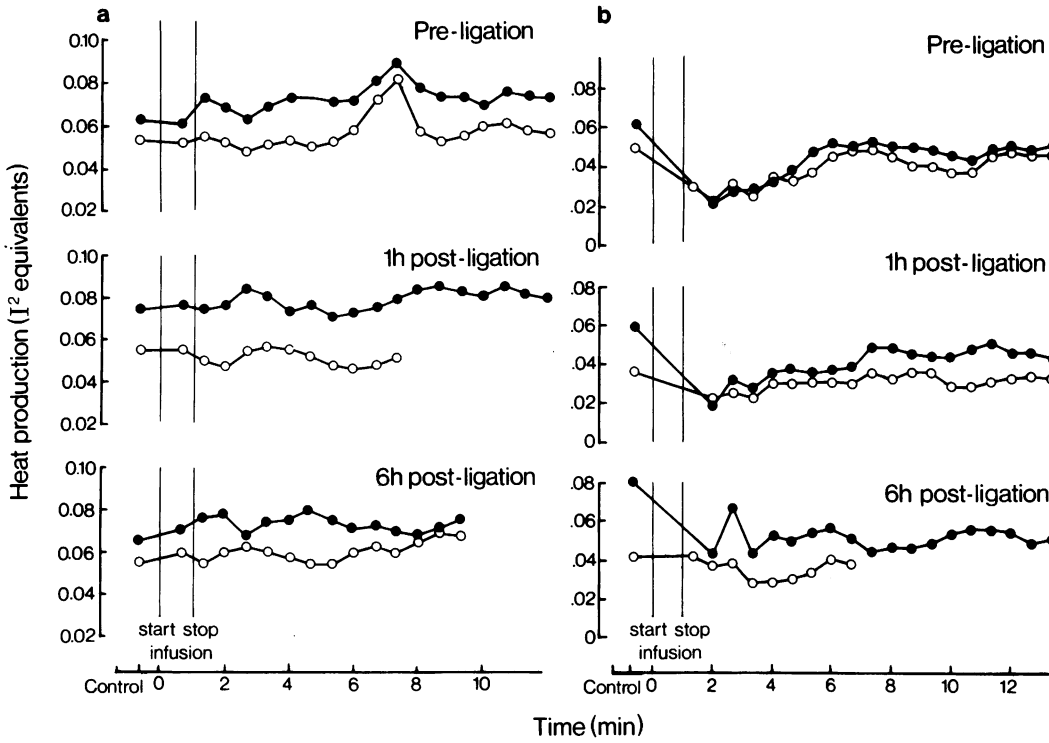

Figure 3 The effect of nitroglycerine (a) and dipyridamole (b) on myocardial heat production (I^2 equivalents) before ligation and 1 and 6 h post-ligation. Proximal myocardium (●); distal myocardium (○).

($P < 0.001$), and at 6 h increased flow by 75% ($P < 0.05$). The 6 h effect was perhaps somewhat minimized by the fact that there was a developing hyperaemia in the area surrounding the zone of ischaemia so that at 6 h control values were 40% higher than pre-ligation control values.

In the distal myocardium prior to ligation, dipyridamole increased local myocardial flow by 74% ($P < 0.05$). After ligation however, the effectiveness of dipyridamole in increasing flow was effectively abolished. At 1 h post-ligation, although Δk increased slightly, this change was not significant. At 6 h no significant change occurred in levels of Δk. Following ligation there was a gradual decline in baseline levels of heat clearance. By 6 h it was 15% below pre-ligation levels.

Discussion

Action of dipyridamole and nitroglycerine on the coronary circulation

Dipyridamole has been described as acting mainly on small resistive arterioles, with little effect on the large conducting arteries of the coronary circulation. Nitroglycerine has been described as acting mainly on large arteries conducting blood towards the microcirculation (Fam & McGregor, 1968). However, in our experiments dipyridamole markedly reduced vascular resistance, having an equal effect on network and post-network vessels, and being equally effective in systole and diastole. The term 'network' describes the subepicardial plexus of vessels larger than 70 μm and includes the main conducting arteries; 'post-network' vessels are the vessels derived from the network and are mainly precapillary and capillary, both superficial and deep. Systolic vascular resistance has a large extravascular component. However, diastolic vascular resistance has been shown to be largely due to blood vessel tone. Our present evidence, therefore, shows that although according to Fam & McGregor (1968) dipyridamole has no dilator action on the large conducting arteries, it does have a pronounced vasodilator action on all other vascular elements of the coronary circulation, dilating network vessels (arteriolar or larger in size) as effectively as post-network vessels. Our evidence also shows that Fam & McGregor

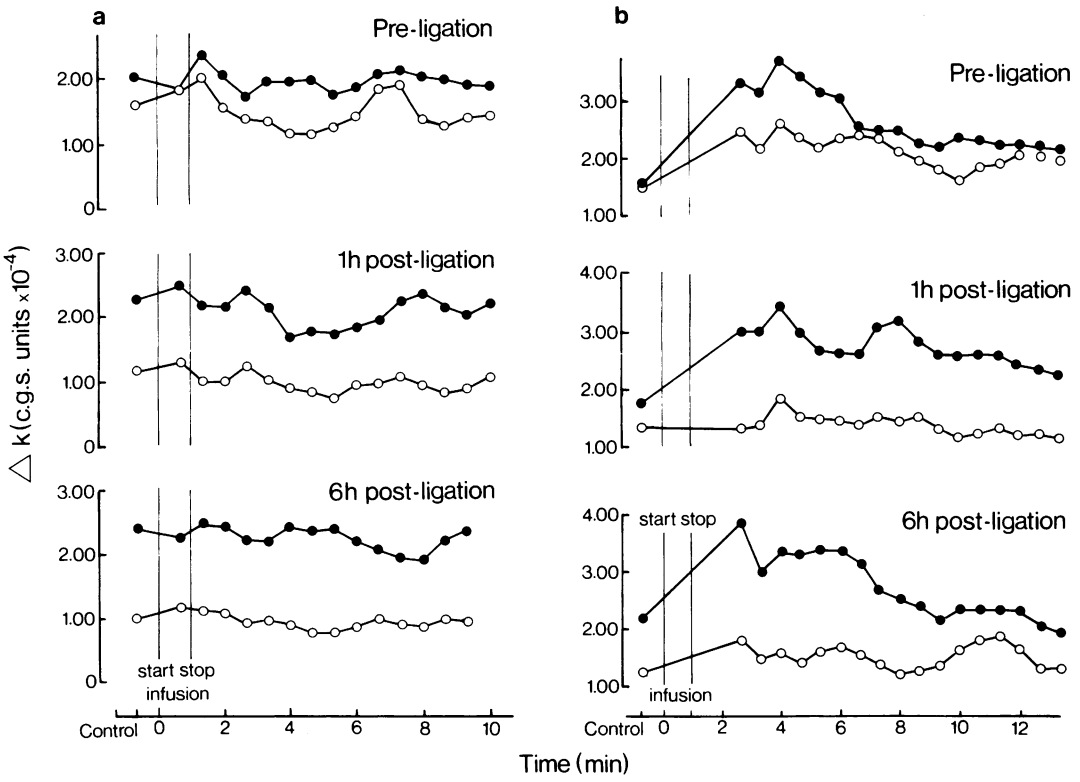

Figure 4 The effect of nitroglycerine (a) and dipyridamole (b) on myocardial heat clearance (Δk) before ligation and 1 and 6 h post-ligation. Proximal myocardium (●); distal myocardium (○).

underestimated the dilator effect of nitroglycerine on the microcirculation. In our experiments nitroglycerine markedly lowered diastolic post-network resistance, showing it to be a marked vasodilator of microcirculatory vessels. However, it was twice as effective in dilating the larger network vessels, which include the conducting arteries referred to by Fam & McGregor. The action of nitroglycerine in systole is more complex. After an initial period of vasodilatation of both network and post-network vessels there followed a variable period of increased resistance. In some cases flow ceased altogether for a very brief period. In general nitroglycerine improved diastolic flow and reduced systolic flow, although heat clearance studies showed little overall effect on tissue blood flow. Since heat production was not significantly affected, it must be assumed that augmented diastolic flow levels compensated for the reduced systolic flow and were sufficient to supply the nutritional needs of the heart. The systolic increase in resistance was probably extravascular arising from increased force of contraction, a baroreceptor response to the 33% fall in blood pressure. The difference between these effects of nitroglycerine and the effects of amyl nitrate which markedly reduced myocardial heat production and increased heat clearance (Grayson, Irvine & Parratt, 1967) should be noted.

The effect of dipyridamole on myocardial heat production

Dipyridamole significantly depressed myocardial heat production in the intact heart. That this is not an artefact due to increased blood flow is shown by the fact that blood flow continued to increase after stabilization of heat production. Moreover in the ischaemic myocardium dipyridamole had no effect on flow; however it still produced significant inhibition of heat production. The metabolic actions of dipyridamole are complex and controversial. There seems to be some agreement however, that dipyridamole prevents the deamination of adenosine (Kübler, Spieckermann & Bretschneider, 1970). It might

not be surprising for the net effect of this to be a diminution in the liberation of free energy from adenosine 5′-triphosphate stores. If this were the case, this might be expected to lead to a reduction in myocardial contractility. However, many investigators report that dipyridamole has no inotropic effect (Kiese, Lange & Resag, 1960; West, Bellet, Manzoli & Müller, 1962), whereas others report increased contractility (Elliot, 1961; Yu & Gluckman, 1969). The most probable conclusion therefore is that dipyridamole, directly or indirectly, leads to increased efficiency of utilization of free energy by the contractile mechanisms. This would decrease the amount of energy lost as heat whilst maintaining the initial force of contraction.

The action of nitroglycerine in the ischaemic myocardium

Heated thermocouple measurements showed that nitroglycerine had little effect on heat clearance or heat production in the ischaemic myocardium. This is similar to earlier findings using xenon clearance (Pasyk, Bloor & Gregg, 1968) and adds weight to the suggestion that the clinical effectiveness of this preparation is independent of its vasodilator properties. It has been suggested that the major factor giving rise to angina or infarction is not so much a total obliteration of blood supply to a tissue, but the generation of a relative hypoxia brought about by a vascular inflow into a region which is insufficient for its work load. The present evidence, therefore, is consistent with the suggestion that nitroglycerine may work through its general action on peripheral resistance which leads to a fall in blood pressure and, consequently, a reduced overall cardiac work load.

The action of dipyridamole in the ischaemic myocardium

In the present experiments, dipyridamole did not improve blood flow to the ischaemic myocardium. This is consistent with the findings of other investigators (Pasyk *et al.*, 1968; Schaper, 1971; Benzing, Wahl, Bender & Rabe, 1973). It has already been observed that in the developing infarct there is a severe reduction of capillary blood flow, possibly due to precapillary vasospasm, with most of the remaining flow passing through larger anastomosing vessels (Grayson & Scott, 1973). This would not be compatible with the 'steal' phenomenon (Fam & McGregor, 1968; Rowe, 1970) in which it is assumed that vessels in the ischaemic area are maximally dilated as a result of hypoxia. However, the vascular changes in acute infarction are probably complex. We have shown that distal to an acute ligation, islands of ischaemic tissue alternate with areas which are well perfused. It is probable that in the well perfused tissue blood vessels are maximally dilated. The clinical ineffectiveness of dipyridamole may well be due to the fact that it is not able to reach the appropriate vascular smooth muscle sites in areas of vasospasm, whereas in the other areas which it can reach blood vessels are already maximally dilated by virtue of hypoxia. In these areas, too, it can lower heat production without further action on blood vessels. It should be noted that heat production which, among other things depends on capillary flow, showed considerable improvement during the 6 h observation period whilst pressures and vascular resistances did not change. Pressure gradients were therefore sufficient for blood delivery through anastomotic routes. This strongly favours an active factor in the initial failure of capillary filling.

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