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The effects of dipyridamole on coronary post-occlusion hyperaemia and on myocardial vasodilatation induced by systemic hypoxia

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Summary

1. The arterial pO_2 of anaesthetized cats was reduced to 33 mmHg by supplying a mixture of oxygen and nitrogen as the respiratory gas. This produced vasodilatation in the myocardial bed which was not increased after the injection of dipyridamole (1 mg/kg).

2. Reactive hyperaemia was observed following occlusion of the left anterior descending coronary artery for 10–120 seconds. The duration of the period of reactive hyperaemia was increased after the injection of dipyridamole. This effect of dipyridamole was most pronounced when the longest periods of occlusion were used.

3. These results support the hypothesis that myocardial reactive hyperaemia is at least partly caused by adenosine released from hypoxic myocardial cells. The vasodilatation occurring during systemic hypoxia, on the other hand, is probably mediated via a different mechanism.

Introduction

It has been proposed that adenosine plays a central role in the regulation of blood flow in the heart (Berne, 1964). Any imbalance between myocardial oxygen requirements and availability (such as might occur during systemic hypoxia or coronary artery occlusion) would result in the increased utilization of adenosine triphosphate, with its consequent degradation to adenosine. According to Berne (1964), adenosine by virtue of its potent vasodilator activity, would increase blood flow and hence oxygen supply to the hypoxic myocardium.

Although several groups have attempted to test this hypothesis with the use of adenosine-sparing drugs, results obtained so far are not entirely consistent. Dipyridamole has been shown to increase coronary reactive hyperaemia in dogs (Bittar & Pauly, 1971a), but lidoflazine was without this effect (Bittar & Pauly, 1971b). However, lidoflazine has been found to augment coronary reactive hyperaemia in miniature pigs (Jageneau, Schaper & Van Gerven, 1969), and Juhran, Voss, Dietmann & Schaumann (1971) found that both dipyridamole and lidoflazine increased coronary reactive hyperaemia in conscious dogs. Lidoflazine does not, however, modify the effects of systemic hypoxia in dogs (Afonso, 1969). In view of these divergent results, it was thought worthwhile to investigate the action of dipyridamole on both coronary reactive hyperaemia and systemic hypoxia. The experiments were performed on anaesthetized cats.

Methods

Cats of either sex were anaesthetized with pentobarbitone and prepared as previously described (Parratt & Wadsworth, 1972). Systemic hypoxia was induced in 6 cats. A mixture of nitrogen and oxygen was supplied via a bag to the inlet of the respiration pump. Blood samples (0·3 ml) were removed from a catheter located in the abdominal aorta. Arterial oxygen tension, and the oxygen tension of the inspired gas mixture, were measured with Radiometer (Copenhagen) electrodes. In each cat, two control periods of hypoxia (5–10 min each) were induced before the injection of dipyridamole and two hypoxic periods after the injection of dipyridamole.

Eight cats were prepared for coronary artery occlusion. The left coronary artery was dissected near its origin and a suture thread passed beneath the left anterior descending branch just distal to the junction with the circumflex branch. When tension was applied to this thread, the artery was occluded for 10–20 seconds. Blood flow was recorded by the use of heated thermocouples, but instead of a cyclic heating current, as used by Parratt & Wadsworth (1972) a constant heating current of 0·2 A^2 was employed. The heated thermocouple, together with its reference junction, was inserted into the myocardium in the region of the left anterior descending artery.

The drugs used were: dipyridamole (Boehringer Ingelheim) and hexobendine (Beecham).

Results

Systemic hypoxia

The arterial pO_2 was reduced by respiring the animals with a mixture of oxygen and nitrogen instead of room air. The relationship between the oxygen tension

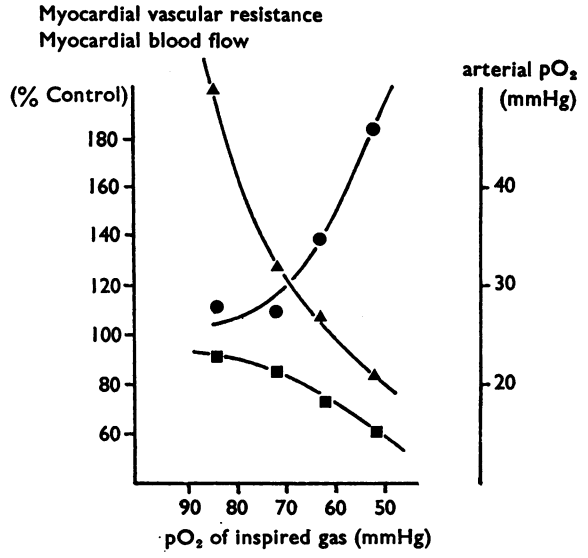

FIG. 1. The effect of systemic hypoxia on myocardial blood flow (●) and vascular resistance (■) in the anaesthetized cat. Flow and resistance are expressed as a percentage of the values observed when room air was respired. The pO_2 of the inspired gas mixture is shown on the abscissae, the equivalent arterial pO_2 (▲) is also plotted. Each point is the mean of three observations. When the arterial pO_2 fell below 30 mmHg there were marked changes in myocardial blood flow and resistance.

of the inspired air and of the arterial blood was constant between animals, and is represented in Figure 1. When the arterial pO_2 fell below 30 mmHg, there was a marked increase in myocardial blood flow, with a corresponding reduction in calculated myocardial vascular resistance. A given level of hypoxia produced large flow increases in some animals, but smaller changes in others; this may have been due to variations in the depth of insertion of the heated thermocouples. Figure 1 shows the average of the flow changes which were observed in three cats. Soon after the start of the hypoxic periods, blood pressure rose; at this time aortic dp/dt was usually also increased. The levels of these parameters then fell to plateaux which were sometimes above and sometimes below control levels. Heart rate was not greatly affected.

In six experiments, systemic hypoxia was induced before and after the intravenous injection of dipyridamole (1 mg/kg). The oxygen tension of the inspired gas was constant throughout any one experiment and averaged (between the 6 cats) 65 ± 6 mmHg (1 mmHg$\equiv$1·333 mbar). Consistent changes in the arterial pO_2 were produced on repeated administration of this gas mixture (see Fig. 2). Systemic

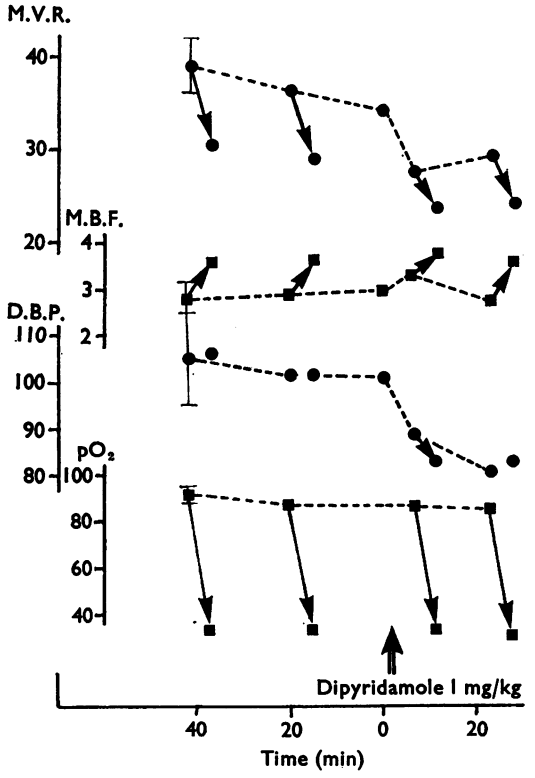

FIG. 2. The effect of dipyridamole on responses to systemic hypoxia in anaesthetized cats. Each point is the mean of six observations; standard error bars have been included for the first measurement. The arrows indicate the mean effects of the four periods of hypoxia that were undergone by each cat. Hypoxia produced a fall in calculated myocardial vascular resistance (arbitrary units; top record), a rise in the myocardial thermal conductivity increment, a measure of blood flow (cal/cm/s/°C; second record), and had little effect on diastolic blood pressure (mmHg; third record). The arterial pO_2 (mmHg) is shown in the bottom record. There was no evidence that the vasodilator effect of hypoxia was augmented after dipyridamole.

hypoxia increased myocardial blood flow by 31±9% and by 27±7% in the two control periods before dipyridamole. Seven minutes after the injection of dipyridamole blood flow increases were 14±8% and 23 min after they were 29±9%. The slightly reduced effect of hypoxia immediately after dipyridamole is probably explained by the fact that the basal level of blood flow was still elevated at this time.

During the control periods of hypoxia, calculated myocardial vascular resistance fell by a mean of 21±4% in these six experiments. There was no evidence of an increased dilator effect after dipyridamole, when resistance fell by 14±12% (7 min) and by 18±5% (22 min). Again, the somewhat reduced effect (where the changes are expressed on a percentage basis) immediately after dipyridamole is probably a reflection of the reduced vascular resistance at this time.

The gradual fall in control levels of myocardial vascular resistance throughout these experiments was partly due to accommodation of vessel tone to changes in blood pressure (Fig. 2). The gradual fall in blood pressure was observed particularly in experiments involving systemic hypoxia and was probably the result of the withdrawal of several samples of blood for analysis.

Artery occlusion

During the occlusion of the left anterior descending branch of the left coronary artery, blood flow dropped rapidly. Haemodynamic effects in some experiments were slight, though in many (especially with longer periods of occlusion) there was a fall in aortic pressure and signs of myocardial ischaemia on the electrocardio-

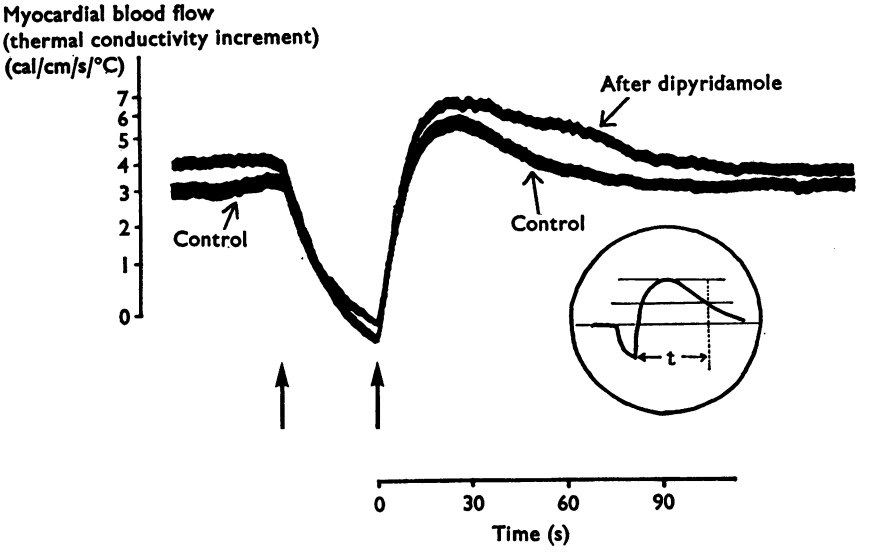

FIG. 3. Reactive hyperaemia following occlusion (marked by arrows) of the left anterior descending artery (superimposition of two records from the same experiment). Myocardial thermal conductivity increment (an index of local blood flow) is shown on the vertical axis. In the inset is shown the method of measurement of the duration of reactive hyperaemia (t) using a construction line drawn through a point where the flow is midway between its maximum and the control level. The lower record is the control response; following occlusion of the left anterior descending artery for 30 s, the reactive hyperaemia lasted for 46 seconds. Four min after the injection of dipyridamole (1 mg/kg), the basal level of blood flow was slightly raised and the duration of reactive hyperaemia was now 65 seconds.

gram. On release of the snare, myocardial blood flow rose transiently to approximately twice the control values. During this period, aortic pressure and aortic dp/dt were frequently above their control levels.

Artery occlusion was performed both before and after the intravenous injection of dipyridamole in 8 cats. The duration of the reactive hyperaemic period was greater after 11 out of 12 injections of dipyridamole (see Fig. 3). The duration of the period of reactive hyperaemia was measured as the time elapsed between release of the snare and the moment when blood flow had returned to a point mid-way between maximum hyperaemic flow and the control flow level before occlusion (Fig. 3).

Although the duration was prolonged, the maximum blood flow attained during the reactive hyperaemia was not increased. Changes in myocardial blood flow and in vascular resistance associated with the hyperaemia following periods of occlusion of 30 s are shown in Figure 4. It is probable that maximal vasodilatation is achieved

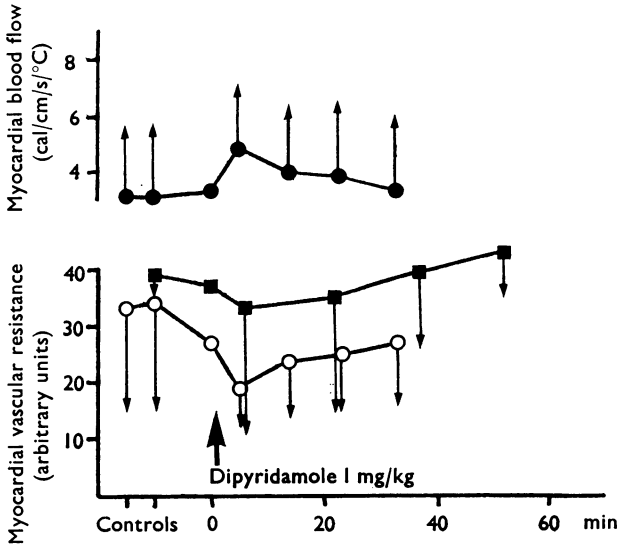

FIG. 4. The effect of dipyridamole on myocardial reactive hyperaemia in anaesthetized cats. The arrows indicate the changes in myocardial thermal conductivity increment, an index of blood flow (●) and in calculated myocardial vascular resistance (○) following occlusion of the left anterior descending artery for 30 seconds. Each is the mean of six results. Two control occlusions were performed, and occlusions were then repeated at various times after the injection of dipyridamole (1 mg/kg). Resistance and flow changes observed during adenosine infusions (■) have been replotted from Parratt & Wadsworth (1972). After dipyridamole the minimal values of resistance recorded were similar during adenosine infusions and during reactive hyperaemia and were probably indicative of maximal vasodilatation.

even after short periods of occlusion (Olsson & Gregg, 1965). This may explain why dipyridamole did not increase the maximum flow, although it did prolong the duration of the hyperaemia.

Reactive hyperaemia was prolonged for up to 25 min following the injection of dipyridamole ; the maximum amount of prolongation was about 3 fold. In contrast, the vasodilator effect of intravenous adenosine infusions are potentiated some 8 fold by dipyridamole, which is active for about one hour (Parratt & Wadsworth, 1972).

In Figure 5 are plotted the average results from experiments in which the left anterior descending artery was occluded for 10 s (7 experiments), 30 s (9 experi-

ments), 60 s (5 experiments) and 120 s (4 experiments). The reactive hyperaemia which followed long periods of artery occlusion appeared to be more markedly prolonged by dipyridamole than was that following shorter periods of occlusion. Thus, the reactive hyperaemia following occlusion for 10 s was only prolonged some 2 fold, and furthermore no prolongation at all could be detected as early as 15 min after the injection of dipyridamole.

In one experiment, hexobendine (0·1 mg/kg) prolonged the reactive hyperaemia following 30 s occlusion by 32%.

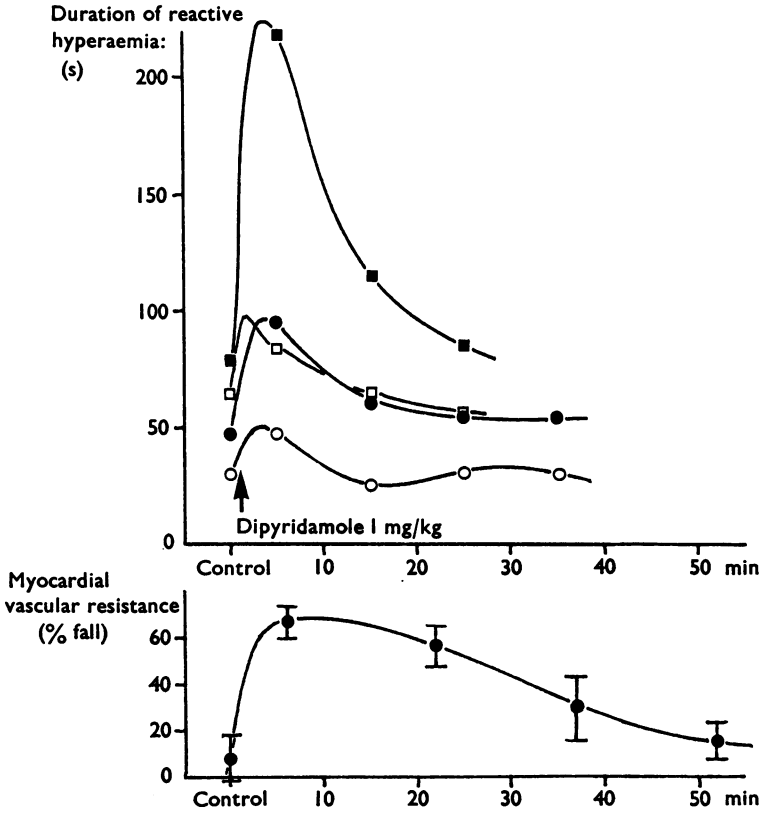

FIG. 5. Prolongation of myocardial reactive hyperaemia at various times following injection of dipyridamole. The vertical axis shows the duration of the reactive hyperaemia following occlusion of the left anterior descending artery for 10 s (○), 30 s (●), 60 s (□) or 120 s (■). Prolongation of hyperaemia following the longest period of occlusion was observed for about 25 min after the injection of dipyridamole. The lower graph shows the potentiation of the vasodilator effect of adenosine (from Parratt & Wadsworth, 1972), which is still detectable 50 min after dipyridamole.

Discussion

There is accumulating evidence that adenosine may be the mediator of the coronary vasodilatation which results from cellular hypoxia in the myocardium. Adenosine, and its breakdown products, hypoxanthine and inosine, appear in the coronary venous blood in elevated amounts during hypoxaemia produced by perfusion with systemic venous blood and reactive hyperaemia (Berne, Rubio, Dobson & Curnish, 1971) and it has been calculated that the extracellular fluid concentra-

tion of adenosine under these conditions would be sufficient to produce maximal dilatation (Rubio, Berne & Katori, 1969). It would therefore be expected that drugs which have an adenosine-sparing action would potentiate the dilatation associated with myocardial hypoxia.

Our results suggest that the duration of the period of coronary reactive hyperaemia following artery occlusion is prolonged by dipyridamole in cats. Dipyridamole has also been found to potentiate coronary reactive hyperaemia in conscious dogs (Bittar & Pauly, 1971a ; Juhran *et al.*, 1971). The duration of action of dipyridamole was surprisingly short when compared with the potentiation of intravenous infusion of adenosine. Further, it is clear from Fig. 5 that, when occlusion periods of 120 s were used, slight prolongation of the reactive hyperaemia period could still be detected 25 min after the injection of dipyridamole. When periods of 10 s were used, the prolonging effect of dipyridamole had already disappeared 15 min after its injection. This dose of dipyridamole potentiates the actions of intravenous adenosine infusions for about one hour (Parratt & Wadsworth, 1972). The more prolonged action in this case is probably because the uptake of adenosine into erythrocytes, which is blocked by dipyridamole, is likely to be a more important inactivating mechanism for intravenously administered adenosine than it is for locally released adenosine.

Reactive hyperaemia following the longer periods of occlusion was more noticeably affected by dipyridamole than that following the shorter periods. Not only was the duration of action of dipyridamole greater after the longer periods of occlusion, but the amount of prolongation was greater (about 3 fold) with periods of 120 s and less with periods of 10 s (about 2 fold). Adenosine, on the other hand, caused an approximately 8 fold greater fall in myocardial vascular resistance after dipyridamole. In these two respects, it seems that the longer periods of occlusion more nearly approximate adenosine infusions in their effects. This may indicate that adenosine only becomes significant in the regulation of blood flow in situations of extremely severe hypoxia, other factors being of primary importance under more ' physiological ' conditions. This conclusion is in line with that of Juhran *et al.* (1971), who found that dipyridamole and lidoflazine only potentiated reactive hyperaemia when the occlusion period had been greater than 30 seconds.

No evidence could be obtained that dipyridamole affected the hypoxaemia occurring in systemic hypoxia (arterial pO_2=33 mmHg). Lidoflazine is also ineffective in altering the raised blood flow of systemic hypoxia (Afonso, 1969). This would suggest that adenosine is not important in the regulation of blood flow under conditions of arterial hypoxaemia. The raised blood flow produced by isoprenaline and by noradrenaline was also not augmented by dipyridamole (Parratt & Wadsworth, 1972). A tentative classification may thus be made on the basis of these experiments. The group of ' less severe ' hypoxic stresses (which are not affected by dipyridamole) would include noradrenaline and isoprenaline administration and systemic hypoxia (arterial pO_2=33 mmHg). Reactive hyperaemia would fall into the ' more severe ' category (dipyridamole sensitive) ; the longer the period of occlusion, the greater the ' more severe ' element it would contain. It appears probable that adenosine is involved in the regulation of myocardial blood flow in these more severe hypoxic stresses.

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