Br. J. Pharmac, (1973), **49**, 391–399.

The effects of dipyridamole on blood flow and oxygen handling in the acutely ischaemic and normal canine myocardium

R. J. MARSHALL AND J. R. PARRATT

Departments of Surgery, University of Glasgow, Western Infirmary, and of Pharmacology, University of Strathclyde, Glasgow

Summary

1. The effects of the intravenous administration of dipyridamole (0·25 mg/kg) were examined in a canine preparation that enabled simultaneous measurements to be made of blood flow in ischaemic and in essentially normal areas of the myocardium and also of oxygen handling (availability, consumption and extraction) in both these regions.

2. When administered to dogs anaesthetized with trichlorethylene 2–3 h after acute ligation of the descending branch of the left coronary artery, dipyridamole markedly increased blood flow in essentially normal regions (left circumflex flow) but failed to increase flow in the area supplied by the ligated vessel (measured by ^{133}xenon clearance and by retrograde flow). In five of the six animals definite decreases in flow ('stealing') were observed in the ischaemic region. These flow changes were related to the decreased trans-ventricular perfusion pressure (diastolic peripheral coronary pressure minus left ventricular end-diastolic pressure) and were accompanied by electrocardiographic evidence of increasingly severe myocardial ischaemia. The results support the suggestion that only increasing the perfusion gradient will usefully improve blood flow (and hence oxygen availability) to the acutely ischaemic myocardium.

3. Despite these effects on ischaemic muscle blood flow, the oxygen tension of the blood draining the infarcting muscle was markedly elevated. The conclusion is drawn that dipyridamole decreases the efficiency of the myocardial circulation by opening up vessels that do not take part in tissue exchange.

Introduction

Myocardial cells begin to die about 20 min after being deprived of their blood supply (Jennings, 1969) and one of the outstanding problems in the therapy of an acute myocardial infarct is the maintenance of flow to viable cells both at the border of, and within, the ischaemic area. There are two possible approaches. One is to maintain perfusion pressure, through whatever collateral vessels are present, either with drugs or by mechanical means such as counter-pulsation. The other is to attempt to dilate existing collateral arterioles with vasodilator drugs, an approach which assumes that such vessels are capable of dilating. This view has received some support from experiments which have provided evidence for a reflex coronary vasoconstriction, triggered by coronary occlusion, and mediated through the sympathetic nervous system (Grayson, Irvine, Parratt & Cunningham, 1968; Grayson, Irvine & Parratt, 1971).

Of the increasing number of coronary vasodilator drugs available most experimental work has been done with dipyridamole (for references and a recent summary of activity see Parratt, 1969). Using a heat clearance technique a number of authors (Kiese, Lange & Resag, 1960; Lange, 1964; Kadatz, 1969; Grayson *et al.*, 1971) have demonstrated that dipyridamole increases flow in experimental infarcts in dogs. This flow change is rather less than that which occurs in normal cardiac muscle. In contrast, in the acutely ischaemic myocardium of both conscious and anaesthetized dogs, dipyridamole does not increase the clearance of either radioactive krypton or xenon (Rees & Redding, 1967; Linder & Seeman, 1967; Pasyk, Bloor, Khouri & Gregg, 1971; Schaper, 1971) except at the border of the ischaemic area (Linder & Seeman, 1967). Few of these studies are, however, relevant to the question of whether it is possible to increase infarct flow with coronary vasodilator drugs at a time when most patients with acute myocardial infarcts present at hospital. Furthermore, there have been no studies on the crucial issue of whether dipyridamole improves oxygen availability, extraction or consumption in the initial few hours of acute myocardial ischaemia. The purposes of this study was to examine the effects of the drug on blood flow and oxygen handling in the acutely ischaemic myocardium (2–3 h post-occlusion) and simultaneously in the surrounding, apparently normal, ventricular muscle.

Methods

Six male greyhounds (mean weight 30 kg) were used for this study. After induction of anaesthesia with intravenous sodium thiopentone (15 to 20 mg/kg) the dogs were intubated and respired with an air mixture (oxygen and nitrogen) containing 0·5 to 1% trichlorethylene vaporized from a Tritec vaporiser (Cyprane Ltd.). The stroke volume of the Palmer respiratory pump was adjusted to give an arterial P_{CO_2} of between 30 and 40 mmHg (mean P_{CO_2} 33 ± 5 mmHg; P_{O_2} 104 ± 5 mmHg). Reflex movement was prevented by the administration of succinylcholine chloride (100 mg by intramuscular injection).

By means of a Siemens' image intensifier, catheters were placed in the descending aorta (by way of the right femoral artery), the right atrium (via the right saphenous vein) and the coronary sinus (via the left external jugular vein) and were used for pressure measurement (with Elema-Schönander capacitance transducers) and for blood sampling. A catheter-tip transducer (Miller Instruments Inc., Houston, Texas) was inserted into the lumen of the left ventricle, by way of the left carotid artery in the neck, and was used for the measurement of left ventricular pressure and dP/dt (using an Elema-Schönander differentiating circuit). Records at high gain allowed assessments to be made of end-diastolic pressure. Cardiac output was measured by dye-dilution. Indocyanine green (2·5 mg) was injected as a bolus into the right atrium and blood withdrawn through a densitometer (Waters Co., Rochester, Minnesota). This blood was later replaced.

The heart was exposed through a left thoracotomy and the pericardium, overlying the anterolateral aspect of the heart, incised. Blood flow in the circumflex branch of the left coronary artery was measured with a Nycotron 372 electromagnetic flowmeter and a 2 mm probe. The anterior descending branch of the left coronary artery, at a point approximately halfway between the tip of the atrium and the apex of the heart, was prepared for ligation with limited dissection. A major branch of the main vein adjacent to the artery (the anterior coronary

vein) was catheterized by the Seldinger technique with a 4 inch Longdwel teflon catheter (size 20 G). This catheter was not tied in position. It will be referred to in the text as the coronary vein catheter and, after coronary artery ligation, has been shown to drain blood predominantly from the ischaemic area (Fisher, Heimbach, Ledingham, Marshall & Parratt, 1973 ; Marshall, Parratt & Ledingham, 1973). Simultaneous anaerobic blood samples were taken at regular intervals from this vein and from the coronary sinus, right atrium and descending aorta. Blood was analysed for oxygen and carbon dioxide tensions, for oxygen content and for pH as outlined by Ledingham, McBride, Parratt & Vance (1970).

After a suitable stabilization period the coronary artery was ligated in one stage. Because ventricular tachycardia leading to fibrillation sometimes occurs after ligation at this site an intravenous injection of lignocaine (20–30 mg) was given two to three minutes prior to ligation. A nylon catheter (Portex, o.d. 1.34 mm) was inserted distally into the ligated vessel and tied in position. This catheter was used for the measurement of peripheral coronary pressure (with another Elema-Schönander transducer) for the measurement of peripheral coronary flow (retrograde or backflow from the open catheter) and for the injection of small amounts of ^{133}xenon into the developing infarct. The clearance of radioactivity from the ischaemic muscle was measured with a collimator having a narrow angle of acceptance. Full details of this method of assessing infarct blood flow are outlined by Rees & Redding (1967) and by Marshall *et al.* (1973). The experimental model used in this study thus allows simultaneous assessments to be made of blood flow in essentially normal regions of the left ventricular wall (left circumflex flow), of infarct blood flow (^{133}xenon clearance and arterial backflow) and of oxygen extraction and consumption in both normal areas of the ventricular wall (coronary sinus sampling) and in the ischaemic area (coronary venous sampling).

Cardiovascular and blood gas changes were monitored for a period of two hours after coronary artery ligation (for details see Marshall *et al.*, 1973) and then an intravenous injection of dipyridamole (Boehringer, Ingelheim) in a dose of 0·25 mg/kg was given. This dose was chosen since, in preliminary experiments, it was shown to markedly increase blood flow to the normal myocardium.

Systemic arterial pressure (pulsatile and meaned by electronic integration), mean right atrial pressure, left ventricular pressure and dP/dt, left ventricular end-diastolic pressure (LVEDP), peripheral coronary pressure (PCP), left circumflex coronary flow and the electrocardiogram (standard limb and epicardial leads) were recorded on an Elema-Schönander ink-jet writing recorder (Mingograph 81). The heart rate was measured from the electrocardiogram.

The following data were derived:

(a) myocardial oxygen extraction coefficients (A–V/A%)

$$= \frac{\text{arterial oxygen content (ml/100 ml)–coronary sinus (or vein) oxygen content (ml/100 ml)}}{\text{arterial oxygen content (ml/100 ml)}} \times 100$$

(b) myocardial oxygen consumption.

(i) normal regions of the left ventricular wall (ml/min)
=left circumflex coronary flow (ml/min)×arterial minus coronary sinus oxygen content

(ii) ischaemic region of the left ventricular wall ((ml/100 g)/min)
=^{133}xenon clearance ((ml/100 g)/min)×arterial minus coronary vein oxygen content

(c) myocardial vascular resistance (normal myocardium)

$$= \frac{\text{diastolic systemic arterial blood pressure (mmHg)}}{\text{coronary (left circumflex) blood flow (ml/min)}}$$

(d) sub-endocardial perfusion pressure (Ledingham, Marshall & Parratt, 1973; the perfusion pressure, during diastole, across the ischaemic wall of the left ventricle)

=diastolic peripheral coronary pressure (mmHg)−LVEDP (mmHg).

Results

The detailed haemodynamic effects of coronary artery ligation in this experimental preparation have already been fully described (Marshall *et al.*, 1973). Two-and-a-half hours after ligation (when the dipyridamole was administered) cardiac output had decreased from the pre-ligation level of 2·5±0·4 litres/min to 1·7±0·3 litres/min ($P<0·05$) whereas mean blood pressure (134±5 before ligation to 132±6 mmHg 2·5 h after ligation), heart rate (178±10 to 193±17 beats/min) and blood flow to areas of the left ventricular wall supplied by the circumflex branch of the coronary artery (70±11 to 68±9 ml/min) were not significantly different from the pre-ligation levels. Blood flow in the area supplied by the ligated artery varied between 10 and 26 (ml/100 g)/min (mean 20±2 (ml/100 g)/min) which is about 20% of the normal (pre-ligation) flow in this area (Marshall *et al.*, 1973; Parratt, Ledingham & McArdle, 1973).

Dipyridamole, in a dose (0.25 mg/kg) that almost doubled blood flow in the normal area of the myocardium, decreased both systemic blood pressure and the pressure in the stump of the ligated artery (peripheral coronary pressure). There were no significant changes in cardiac output, heart rate, right atrial pressure, left ventricular dP/dt *max* or LVEDP. The haemodynamic effects are summarized in Table 1. The most pronounced effect of dipyridamole was a markedly increased blood flow in the area supplied by the circumflex artery (Table 2 and Fig. 1), an effect which lasted for between 20 and 35 minutes. At the time when blood

TABLE 1. *The haemodynamic effects of dipyridamole* (10 *min after* 0.25 *mg/kg*) *when administered to dogs* 2–3 *h after acute coronary artery ligation*

	Control	After dipyridamole
Systemic blood pressure (mmHg)		
systolic	156±8	118±14†
diastolic	117±6	86±12†
mean	132±5	97±13†
Peripheral coronary pressure (mmHg)		
systolic	60±6	41±5†
diastolic	20±5	10±2§
mean	36±3	25±4*
Heart rate (beats/min)	193±17	182±16 NS
Cardiac output (l/min)	1·5±0·3	1·2±0·3 NS
External cardiac work (kgm/min)	2·8±0·5	1·7±0·4§
Left ventricular dP/dt *max.* (mmHg/s)	2,780±460	2,230±260 NS
LVEDP (mmHg)	10·8±2·5	9·4±1·7 NS

Values are mean±S.E.M. * $P<0·005$; † $P<0·01$; § $P<0·05$.

flow had returned to normal however systemic blood pressure was still decreased. Twenty minutes after the injection the diastolic pressure was a mean of 32 mmHg below the pre-injection level; 40 min after injection it was 20 mmHg below. Full recovery was only rarely obtained. These results confirm the observations that dipyridamole markedly reduces normal myocardial vascular resistance. Coronary sinus PO_2 was markedly elevated by the drug in one dog reaching a level of 62 mmHg) whilst myocardial oxygen extraction and calculated oxygen consumption were decreased. These effects persisted after left circumflex flow had returned to pre-injection levels (see Figure 1).

In all except one experiment, infarct (nutritive) blood flow (^{133}xenon clearance) was decreased after dipyridamole (Figure 2). There was a good relationship between this change in infarct blood flow and the change in sub-endocardial perfusion pressure (diastolic peripheral coronary pressure minus LVEDP, that is, the perfusion gradient across the ischaemic ventricular wall). The decrease in

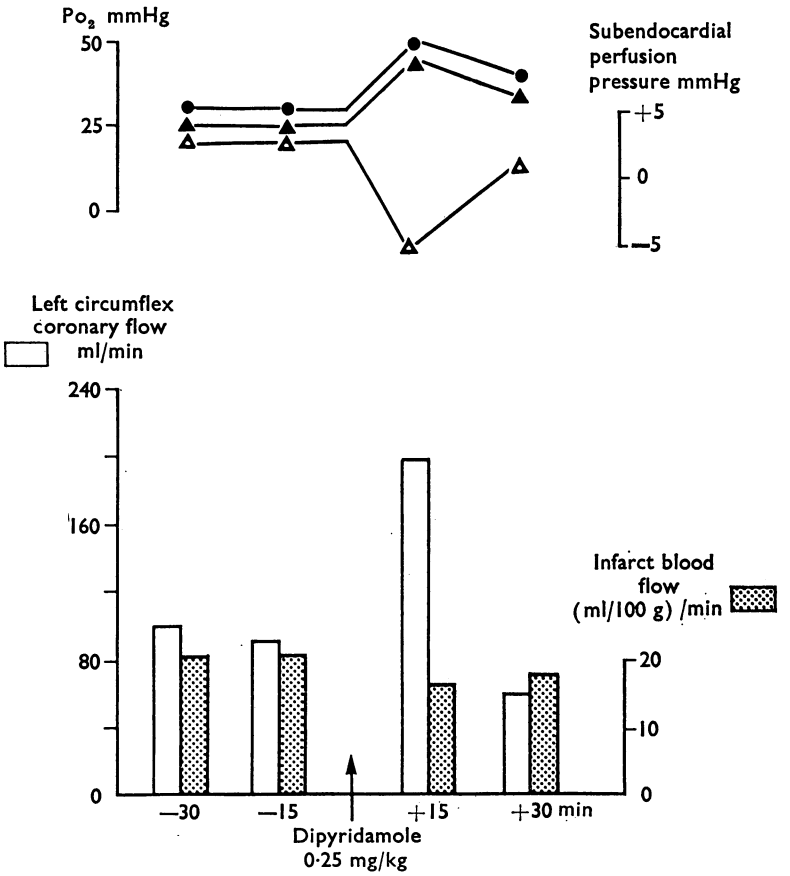

FIG. 1. The typical effects of dipyridamole 0·25 mg/kg i.v., when given 2·5 h after coronary artery ligation, showing that although blood flow in the normal area (□) of myocardium increases, that in the ischaemic area (⁝⁝) tends to decrease. There is however an increase in the P_{O2} of both coronary sinus blood (▲; draining essentially normal myocardium) and coronary venous blood (●; draining the ischaemic myocardium). The decrease in blood flow is associated with a reduction in the driving pressure across the left ventricular wall, the sub-endocardial perfusion pressure (△).

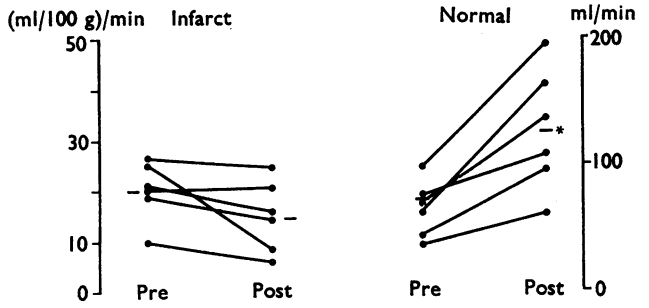

FIG. 2. The effects of dipyridamole on blood flow simultaneously measured in normal (on the right) and ischaemic (on the left) areas of myocardium in six greyhounds. Dipyridamole fails to increase flow in the developing infarct in a dose that markedly increases flow in the normal region. *$P<0.005$.

sub-endocardial driving pressure was greatest (20 mmHg) in the dog which showed the most marked decrease in infarct blood flow ((16 ml/100 g)/min) and the only experiment in which sub-endocardial driving pressure was increased after dipyridamole (by 2·5 mmHg) was also the only experiment where ^{133}xenon clearance increased (by 5%). Despite the decreased ^{133}xenon clearance after dipyridamole the oxygen tension in the blood draining the ischaemic region was markedly elevated (Table 2 and Figure 1) and the venous P_{CO_2} was decreased (Table 2). Again the effect on blood gases lasted longer than the effect on ischaemic muscle blood flow (Figure 1). Despite the decrease in P_{CO_2} the venous blood became more acidic after dipyridamole, the calculated base excess falling from a mean of −0·03 to −1·4 mEq/litre.

In all except one experiment the depression of the ST segment of the electrocardiogram, characteristic of myocardial ischaemia in this preparation, worsened after the administration of dipyridamole (Figure 3). Before the drug the mean ST depression was 540 μV; after it was 840 μV. This increase in the severity of myocardial ischaemia was accompanied by occasional ventricular extrasystoles.

TABLE 2. *Myocardial vascular and metabolic effects of dipyridamole (0·25 mg/kg) when administered 2–3 h after acute coronary artery ligation (mean±S.E.)*

	Control	After dipyridamole
Normal area of the left ventricular wall		
Blood flow (ml/min)	68±9	132±22*
Vascular resistance (arbitrary units)	2·19±0·28	0·89±0·23*
Oxygen availability (ml/min)	13·3±1·8	25·1±4·5†
Oxygen extraction coefficient (%)	60±4	22±4*
Coronary sinus P_{O_2} (mmHg)	25±2	46±6*
Coronary sinus P_{CO_2} (mmHg)	43±5	34±2§
Ischaemic area of the left ventricular wall		
Blood flow (^{133} xenon clearance (ml/100 g)/min)	20±2	15±3
Peripheral coronary flow (ml/min)	1·8±0·3	1·3±0·2
Vascular resistance (arbitrary units)	1·78±0·33	1·93±0·41
Oxygen availability ((ml/100 g)/min)	4·0±0·4	2·8±0·6†
Oxygen extraction coefficient (%)	52±5	26±8†
Coronary vein P_{O_2} (mmHg)	27±1	42±4†
Coronary vein P_{CO_2} (mmHg)	45±6	38±5§

*$P<0.005$; †$P<0·01$; §$P<0·05$.

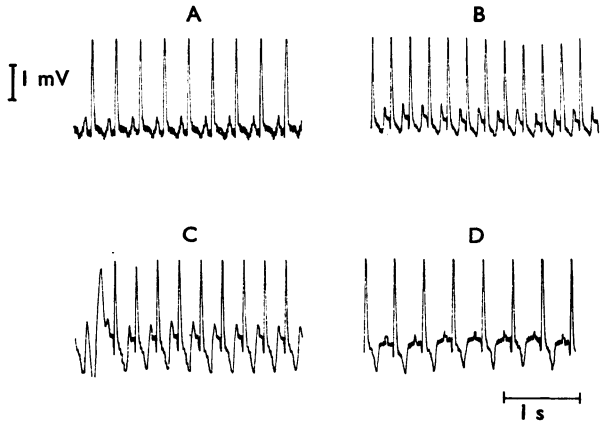

FIG. 3. Electrocardiographic (limb lead II) changes associated with ligation and dipyridamole: A. Before ligation of the LAD coronary artery. B. 2·5 h post-ligation and immediately prior to injection of dipyridamole. C. 5 min post-dipyridamole when normal blood flow maximally increased. D. 15 min post-dipyridamole. Although at this time flow in normal areas of the myocardium had returned to control levels, the ST segment changes in ECG suggest that the myocardium is more ischaemic than before administration of the drug (panel B).

Discussion

Most previous studies have been concerned with the effects of dipyridamole on blood flow in an area of myocardium made *chronically* ischaemic by the gradual occlusion of a major coronary artery (Fam & McGregor, 1965 ; Kadatz, 1969). The present studies are concerned with the effects of the drug on blood flow and oxygen handling after 2–3 h of ischaemia and are relevant to the problem of whether it is possible, by pharmacological means, to improve oxygen availability to an ischaemic area within the first few hours of an infarction. The results demonstrate conclusively that, whilst the intravenous administration of dipyridamole within 3 h of acute coronary artery ligation is able to improve blood flow markedly (and hence oxygen availability) to the normal areas of myocardium adjacent to the ischaemic region, it is unable to improve oxygen availability to the infarct itself. In fact there was evidence in most of the experiments of a 'stealing' phenomenon similar to that outlined by Fam and McGregor (Fam & McGregor, 1964 ; 1967 ; McGregor, 1966) for the myocardium rendered chronically ischaemic over a period of about 3 weeks. In all except one experiment infarct blood flow fell after dipyridamole. We believe this result to be pharmacologically significant because (a) infarct blood flows remain remarkably constant in the same canine preparation over several hours (Marshall *et al.*, 1973), and (b) infarct flows returned to the pre-dipyridamole levels about 30 min after the injection (see Figure 1). This decrease in infarct blood flow was similar whether measured by the backflow method (retrograde or peripheral coronary flow) or by radioactive xenon clearance and probably reflects the reduced perfusion pressure. We have previously suggested (Ledingham, Marshall & Parratt, 1973) that blood flow in the acutely ischaemic myocardium is primarily a function of the perfusion (driving) pressure across the left ventricular wall. The present studies support this hypothesis. Dipyridamole significantly lowered peripheral coronary pressure (Table 1) without changing LVEDP which means that the driving pressure across the ischaemic part of the left ventricular wall was reduced.

There have been no previous studies in which attempts have been made to sample venous blood from the ischaemic area after the administration of

dipyridamole. Before coronary artery ligation the coronary venous catheter (draining the area of the left ventricular wall supplied predominantly by the terminal branches of the anterior descending artery) and the coronary sinus catheter, drain from metabolically similar regions (Fisher *et al.*, 1973; Marshall *et al.*, 1973). Immediately after ligation in this experimental model, marked changes occur in coronary venous blood which do not occur in coronary sinus blood. These include lactate production, an elevation in P_{CO2} and decreases in pH, P_{O2} and in oxygen content (Fisher *et al.*, 1973; Marshall *et al.*, 1973). There is thus no doubt that the coronary venous catheter is draining venous blood from the infarcting area. Dipyridamole not only markedly increased coronary sinus P_{O2} but also increased the P_{O2} of the coronary venous blood draining the ischaemic area (Table 2 and Figure 1). The increased coronary sinus P_{O2} (and decreased P_{CO2}) presumably reflects an increased blood flow to normal areas of the left ventricular wall. This clearly cannot be the explanation for the elevated coronary venous P_{O2}. One possible explanation for this effect is that the drug is opening up vessels which do not take part in tissue exchange and that the 'efficiency' of the circulation (that is, the ratio of exchange function to total blood flow within the ischaemic area) is decreased. The fact that the effects of dipyridamole on coronary sinus P_{O2} lasted longer than its effects on left circumflex flow suggests such 'shunt' channels are opened up by the drug in normal areas of the myocardium as well as in the ischaemic area. A disproportionate increase in total (shunt and nutritional) as opposed to nutritional flow alone, has also been described in the normal myocardium by Tillich, Mendoza & Bing (1971) for noradrenaline and nicotine and, in the ischaemic myocardium, by Parratt *et al.* (1973) for the coronary vasodilator drug, carbochromen. The observed dipyridamole-induced stealing of blood from capillaries in the ischaemic area may thus arise through arteriolar vasodilatation in normal areas of the myocardium (as proposed by Fam & McGregor, 1964) as well as by 'shunting' within the ischaemic area itself. This would account for the finding that heat clearance is increased by dipyridamole in the acutely ischaemic canine preparation (Grayson *et al.*, 1971). One would expect all blood vessels (nutritive and shunt) to permit the transfer of heat energy.

These experiments show that there is no justification for the use of dipyridamole given for the purpose of increasing oxygen availability to the acutely ischaemic myocardium. Oxygen availability is in fact *decreased* by the drug, a fact that might explain the increased severity of the ischaemic pattern observed in the electrocardiogram. Furthermore, these results support the suggestion that the blood vessels of the nutritional circulation are maximally dilated in the developing infarct and that only changes in perfusion pressure will usefully improve flow (and hence oxygen availability) to the acutely ischaemic myocardium (Ledingham *et al.*, 1973).

This work was supported by a joint grant (HERT 345) to Drs. J. R. Parratt and I. McA. Ledingham from the Scottish Hospitals Endowments Research Trust. We are also grateful for the able technical assistance of Messrs. I. Douglas, K. Gorman and R. Thomson.

REFERENCES

FAM, W. M. & MCGREGOR, M. (1964). Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. *Circulation Res.*, **15**, 355–365.

FAM, W. M. & MCGREGOR, M. (1967). The role of collateral circulation in evaluation of antianginal drugs. In: *Problems in laboratory evaluation of antianginal agents*, ed. Winbury, M. M. Amsterdam: North-Holland.

FISHER, W., HEIMBACH, D., LEDINGHAM, I. McA., MARSHALL, R. J. & PARRATT, J. R. (1973). Blood flow and oxygen extraction in ischaemic and normal regions of the myocardium following acute coronary artery ligation. *J. Physiol., Lond.*, **229**, 15–17*P*.

GRAYSON, J., IRVINE, M. & PARRATT, J. R. (1971). Effects of carbochromen and dipyridamole on blood flow and heat production in the normal and ischaemic canine myocardium. *Cardiovasc. Res.*, **5**, 41–47.

GRAYSON, J., IRVINE, M., PARRATT, J. R. & CUNNINGHAM, J. (1968). Vasospastic elements in myocardial infarction following coronary occlusion in the dog. *Cardiovasc. Res.*, **2**, 54–62.

JENNINGS, R. B. (1969). Early phase of myocardial ischemic injury and infarction. *Am. J. Cardiol.*, **24**, 753–765.

KADATZ, R. (1969). Sauerstoffdruck und Durchblutung im gesunden und koronarinsuffizienten Myokard des Hundes und ihre Beeinflussung durch koronarerweiternde Pharmaka. *Arch. Kreislaufforsch.*, **58**, 263–293.

KIESE, M., LANGE, G. & RESAG, K. (1960). Die Wirkung von 2,6-Bis(diäthanolamino)-4,8-dipiperidinopyrimido (5,4-d)pyrimidin auf die Durchblutung des experimentellen Herzinfarkts und des gesunden Herzmuskels. *Z. ges. exp. Med.*, **132**, 426–435.

LANGE, G. (1964). Beeinflussung der Durchblutung des experimentellen Herzinfarkts durch einige gefässerweiternde und blutdrucksteigernde Arzneimittel. *Fortschr. Med.*, **82**, 561–565.

LEDINGHAM, I. McA., MARSHALL, R. J. & PARRATT, J. R. (1973). Drug-induced changes in blood flow in normal and ischaemic regions of the canine myocardium. *Br. J. Pharmac.*, **47**, 626–627*P*.

LEDINGHAM, I. McA., McBRIDE, T. I., PARRATT, J. R. & VANCE, J. P. (1970). The effect of hypercapnia on myocardial blood flow and metabolism. *J. Physiol., Lond.*, **210**, 87–105.

LINDER, E. & SEEMAN, T. (1967). Effects of Persantin and nitroglycerin on myocardial blood flow during temporary coronary occlusions in dogs. *Angiologica*, **4**, 225–255.

McGREGOR, M. (1966). Do vasodilators benefit patients who have ischemic heart disease? *J. Am. Med. Ass.*, **195**, 29–33.

MARSHALL, R. J., PARRATT, J. R. & LEDINGHAM, I. McA. (1973). Changes in blood flow and oxygen consumption in normal and ischaemic regions of the myocardium following acute coronary artery ligation. *Cardiovasc. Res.*, **7** (in press).

PARRATT, J. R. (1969). Pharmacological aspects of the coronary circulation. In: *Progress in medicinal chemistry*, ed. Ellis, G. P. & West, G. B., **6**, pp. 11–66. London: Butterworths.

PARRATT, J. R., LEDINGHAM, I. McA. & McARDLE, C. S. (1973). The effect of a coronary vasodilator drug (carbochromen) on blood flow and oxygen extraction in acute myocardial infarction. *Cardiovasc. Res.*, **7**, 401–407.

PASYK, S., BLOOR, C. M., KHOURI, E. M. & GREGG, D. E. (1971). Systemic and coronary effects of coronary artery occlusion in the unanaesthetized dog. *Am. J. Physiol.*, **220**, 646–654.

REES, J. R. & REDDING, V. J. (1967). Effects of dipyridamole on anastomotic blood flow in experimental myocardial infarction. *Cardiovasc. Res.*, **1**, 179–183.

SCHAPER, W. (1971). *The collateral circulation of the heart*. Amsterdam: North-Holland.

TILLICH, G., MENDOZA, L. & BING, R. J. (1971). Total and nutritional coronary flow. *Circulation Res.*, **28** and **29**, Supplement **1**, 148–153.

(*Received March* 21, 1973)