Brit. J. Pharmacol. (1966), **26**, 713–722.

EFFECTS OF ADRENALINE AND NORADRENALINE ON CORONARY BLOOD FLOW BEFORE AND AFTER BETA-ADRENERGIC BLOCKADE

BY

P. G. GAAL, A. A. KATTUS, A. KOLIN AND G. ROSS

From the Departments of Medicine and Biophysics, University of California, Los Angeles

(*Received November* 16, 1965)

There are conflicting reports regarding the actions of adrenaline and noradrenaline on the coronary circulation. Some studies (Feinberg & Katz, 1958; Denison, Bardhanabaedya & Green, 1956) have indicated that these agents are solely coronary vasodilators, while others (Berne, 1958) have suggested that their primary action is vasoconstriction and that the increased coronary flow usually observed is secondary to metabolic changes associated with stimulation of the myocardium. Berne (1958) has stated that previous failures to demonstrate primary vasoconstriction may have been due to inadequate methodology. The present paper reports the use of electromagnetic flow meters and non-cannulating probes to determine the effects of adrenaline and noradrenaline on coronary arterial flow. The method enables rapid flow changes to be detected with minimum disturbance to the coronary vascular bed and also permits evaluation of changes in extravascular compression induced by the amines. Further clarification of the adrenergic mechanisms was obtained by comparing the effects of adrenaline and noradrenaline before and after blockade of the beta-adrenergic receptors by pronethalol and propranolol.

METHODS

Fourteen dogs weighing 18–28 kg were used. Technically satisfactory results were obtained in 12. Anaesthesia was produced by intravenous sodium pentobarbitone 30 mg/kg. After a median sternotomy, the pericardium was opened and the ascending aorta and 1–2 cm lengths of the proximal parts of the right coronary artery and the anterior descending branch of the left coronary artery were separated from adjacent tissues. Blood flow in these vessels was measured simultaneously by gated sine-wave electromagnetic flow meters (Kolin & Kado, 1959) with non-cannulating probes (Cox, Arora & Kolin, 1963). In three dogs flow was also measured in the left circumflex coronary artery. Zero flow levels for the coronary arteries were obtained by momentarily occluding each artery immediately distal to its probe. Electrical zeros were not used. The baselines were frequently checked throughout the procedures. The probes were calibrated with saline delivered by a gravity feed.

Pressure in the ascending aorta was recorded via a catheter inserted into a common carotid artery and positioned just distal to the aortic probe.

Positive pressure ventilation was maintained by a Bird Mark 8 respirator, which delivered a mixture of oxygen and atmospheric air. The oxygen content of the mixture was approximately 40%.

Intracoronary injections were given as "slugs" by a microsyringe connected to an indwelling 30-gauge needle. This needle produced no measurable alteration of mean or instantaneous coronary flow. The volume of each injection was kept below 0.02 ml. since it was found that saline injections exceeding this volume occasionally produced a slight increase in coronary blood flow. Intravenous injections were administered as "slugs" via a catheter in an external jugular vein. Adrenaline and noradrenaline were given in the form of adrenaline chloride (Parke Davis) and Levophed (Winthrop). Beta-adrenergic blockade was produced by intravenous pronethalol (Alderlin, Ayerst Laboratories) 1 mg/kg or propranolol (Inderal, Ayerst Laboratories) 0.25 mg/kg. Doses are expressed in terms of base.

RESULTS

Control values. The dogs used varied in species, age, weight and sex and a wide range of coronary flows was therefore observed. Left anterior descending flow ranged from 14 to 41 ml./min, left circumflex flow from 42 to 60 ml./min and right coronary flow from 8 to 34 ml./min. These values are similar to those reported by Gregg & Fisher (1963) in anaesthetized open-chest dogs. The instantaneous flow patterns of the left coronary vessels closely resembled those published by Gregg, Khouri & Rayford (1965). Systolic flow in the branches of the left coronary artery was often appreciable and sometimes amounted to as much as 45% of diastolic flow. The instantaneous flow pattern of the right coronary artery was similar to that obtained by us in a previous study (Kolin, Ross, Gaal & Austin, 1964).

Effects of intracoronary adrenaline and noradrenaline. Both agents produced similar changes in doses of 0.5 to 2.0 μg. The development of the response to noradrenaline is shown in Fig. 1,*A*. Flow increased in the injected artery in all of five animals. The increase occurred in two stages. During the first (Stage I), which began 3–4 sec following injection and lasted 2–3 sec, both systolic and diastolic coronary flow increased. In the next stage (Stage II) systolic flow progressively decreased and eventually reversed while diastolic flow increased further. These changes are clearly seen in Fig. 2, which is made up of enlargements of appropriate portions of Fig. 1. The maximum increase in end-diastolic coronary flow was reached about 20 sec following injection. Thereafter end-diastolic flow decreased and systolic flow increased until the pre-injection instantaneous flow pattern was restored some 2 min after injection. No change in heart rate, arterial pressure, duration of systole or peak aortic flow occurred during Stage I but in Stage II the duration of systolic ejection decreased and peak aortic flow increased (Fig. 3). When adrenaline or noradrenaline were injected into the left anterior descending coronary artery no change in flow occurred in the right coronary artery but the left circumflex artery showed the changes of Stage II although to a lesser extent than the injected artery.

After beta-adrenergic blockade produced by intravenous pronethalol or propranolol, intracoronary adrenaline or noradrenaline produced a reduction of both systolic and diastolic flow in the injected artery during Stage I. During Stage II, the increase of coronary diastolic flow and the further reduction of systolic flow either did not occur or were greatly attenuated Fig. 1,*B*, 2,*B*). Manifestations of myocardial stimulation, namely, shortening of systolic ejection and increase in peak aortic flow velocity were absent or reduced.

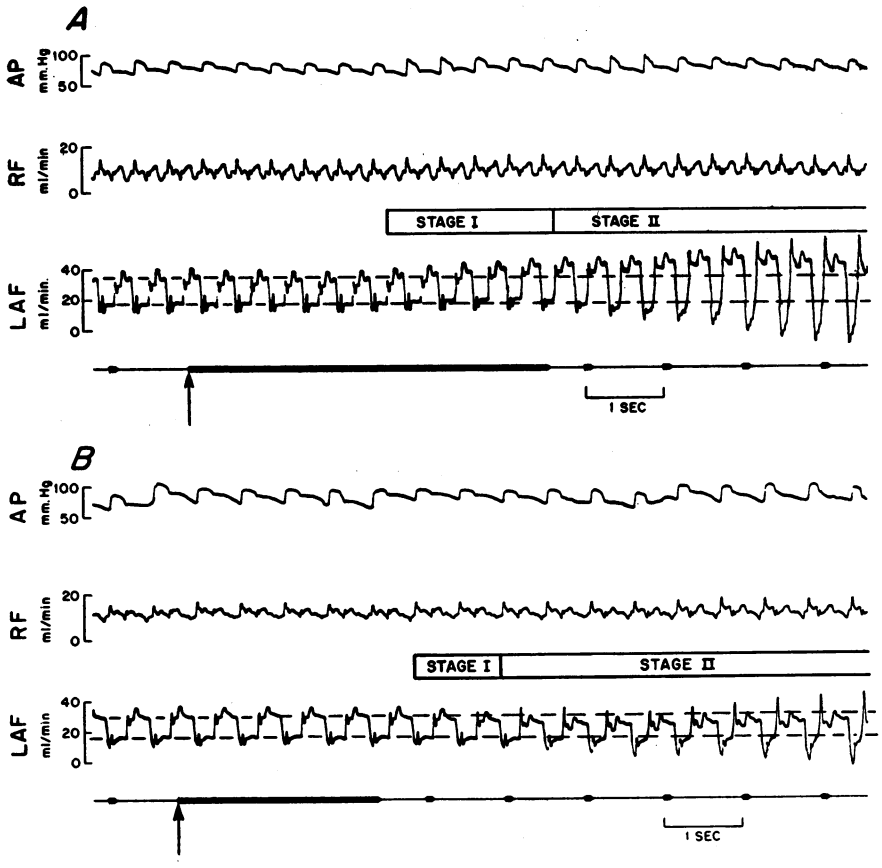

Fig. 1. Effects of injection of 2 μg noradrenaline into left anterior descending coronary artery (LAF) before and after beta-adrenergic blockade. No changes are produced in right coronary flow (RF) or aortic pressure (AP). The dotted lines indicate the highest levels of end-systolic and end-diastolic flow in the injected artery during the pre-injection period. Arrow indicates moment of injection. Upper traces (*A*). Before beta-adrenergic blockade. During Stage I of the response both systolic and diastolic flows increase. During Stage II systolic flow is reduced and then reversed while diastolic flow increases still further. Lower traces (*B*). After beta-adrenergic blockade produced by intravenous propranolol 1 mg/kg. Within 3 sec of the injection both systolic and diastolic coronary flows decrease.

The changes in coronary vascular resistance ($\frac{\text{end-diastolic aortic pressure}}{\text{end-diastolic coronary flow}}$) produced during Stage I by adrenaline and noradrenaline before and after beta-adrenergic blockade are shown in Table I.

Effects of pronethalol and propranolol. Intracoronary injection of these substances transiently increased systolic and diastolic flow in the injected vessel. The effect usually lasted less than 20 sec. The threshold dose for pronethalol was 100–200 μg and for propranolol 10–20 μg. The highest doses used (pronethaolol 500 μg, propranolol 100 μg) reduced coronary vascular resistance by approximately 50%. These doses produced no alteration of heart rate, aortic pressure or cardiac output.

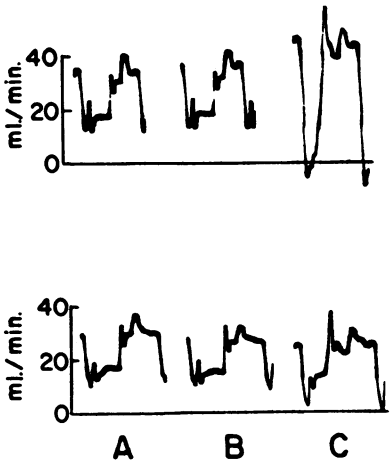

Fig. 2. Effects of injection of 2 μg noradrenaline injected into the left anterior descending coronary artery on the instantaneous flow pattern of this artery. Upper trace. Before beta-adrenergic blockade. Lower trace. After beta-adrenergic blockade. A, immediately preceding injection; B, 4 sec later; C, 9 sec later.

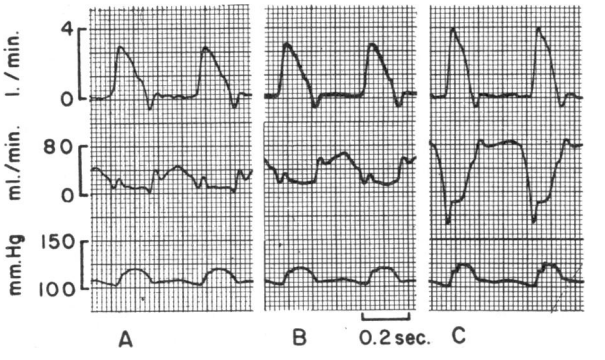

Fig. 3. Effects of noradrenaline injected into the left anterior descending coronary artery on the instantaneous flow patterns of the ascending aorta (upper trace) and left anterior descending coronary artery (middle trace). Bottom trace, aortic pressure. A, immediately before injection; B, 4 sec later (during Stage I); C, 9 sec later (during stage II).

TABLE 1

MAXIMUM PERCENTAGE CHANGES IN CORONARY VASCULAR RESISTANCE DURING STAGE I OF RESPONSE TO INTRACORONARY ADRENALINE (2 μG) AND NORADRENALINE (2 μG) IN SEVEN DOGS BEFORE AND AFTER BETA-ADRENERGIC BLOCKADE

" — " Indicates not tested

Before beta-adrenergic blockade		After beta-adrenergic blockade	
Adrenaline	Noradrenaline	Adrenaline	Noradrenaline
−19	—	0	—
−27	− 9	—	+ 13
−50	−25	+150	+300
−20	−10	+ 10	+ 16
−18	−18	+ 13	0
−40	−16	—	—
−11	−15	+ 25	+ 25

Intravenous pronethalol 1 mg/kg produced prolonged bradycardia and transient hypotension. Coronary flow diminished in all animals in association with the hypotension but coronary vascular resistance did not change. In two animals, a slight increase in coronary flow preceded the reduction in pressure. Intravenous propranolol 0.25 mg/kg produced similar effects except that the hypotension was less marked.

Effects of intravenous adrenaline and noradrenaline. In doses of 1 μg/kg these agents increased blood flow in the three major coronary arteries. The same distinct stages occurred (Fig. 4,*A*) as after intra-arterial administration. During Stage I, which began

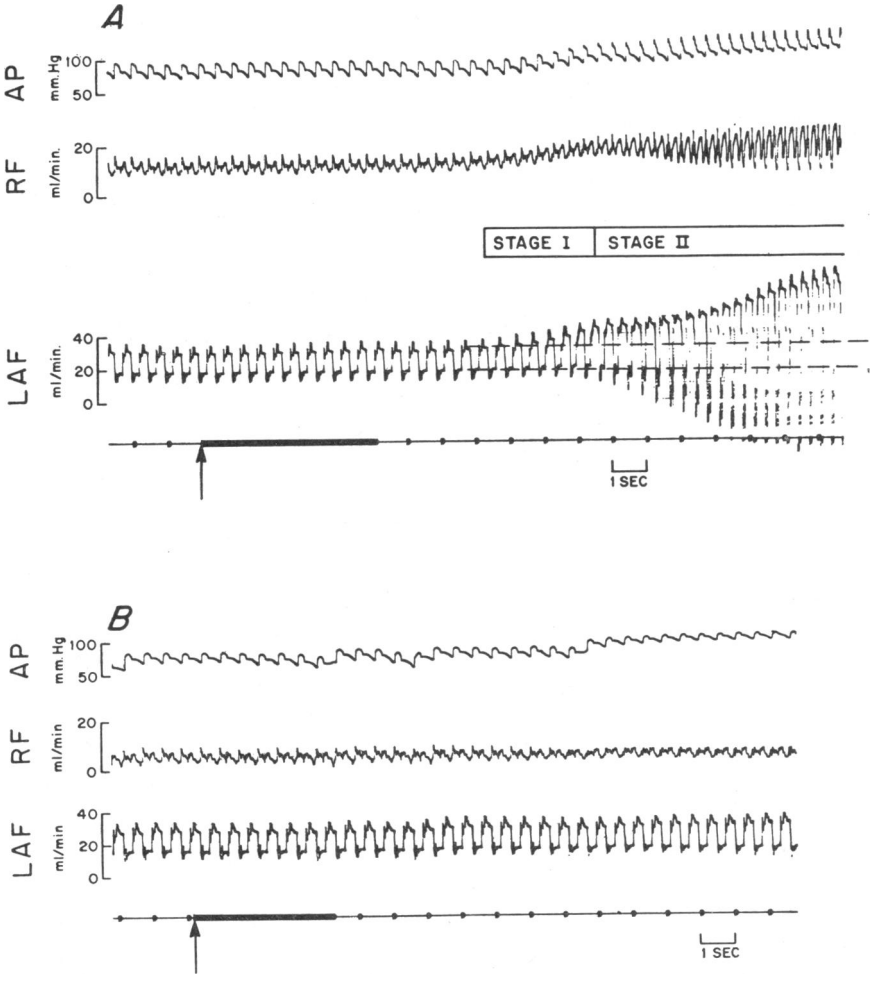

Fig. 4. Effects of intravenous noradrenaline 20 μg on flow in the right coronary artery (RF) and left anterior descending coronary artery (LAF) and on aortic pressure (AP). Upper traces (*A*). Before beta-adrenergic blockade. The dotted horizontal lines indicate the levels of greatest end-diastolic and end-systolic flow in the left anterior descending coronary artery during the pre-injection period. Lower traces (*B*). After beta-adrenergic blockade produced by propranolol 1 mg/kg.

7–9 sec after injection and lasted 2–4 sec, both systolic and diastolic coronary flows increased in the absence of changes in heart rate or duration of systole. The increase in flow produced by adrenaline frequently preceded the rise of aortic pressure. Noradrenaline increased coronary flow and aortic pressure concurrently. During Stage II the duration of systole decreased while heart rate, peak aortic flow velocity and cardiac output increased. Systolic coronary flow decreased in all the coronary vessels and was eventually reversed in the branches of the left coronary artery but not in the right coronary artery. Despite the reduction of systolic flow in all three major coronary arteries mean flow in these vessels increased because of a further rise in diastolic flow.

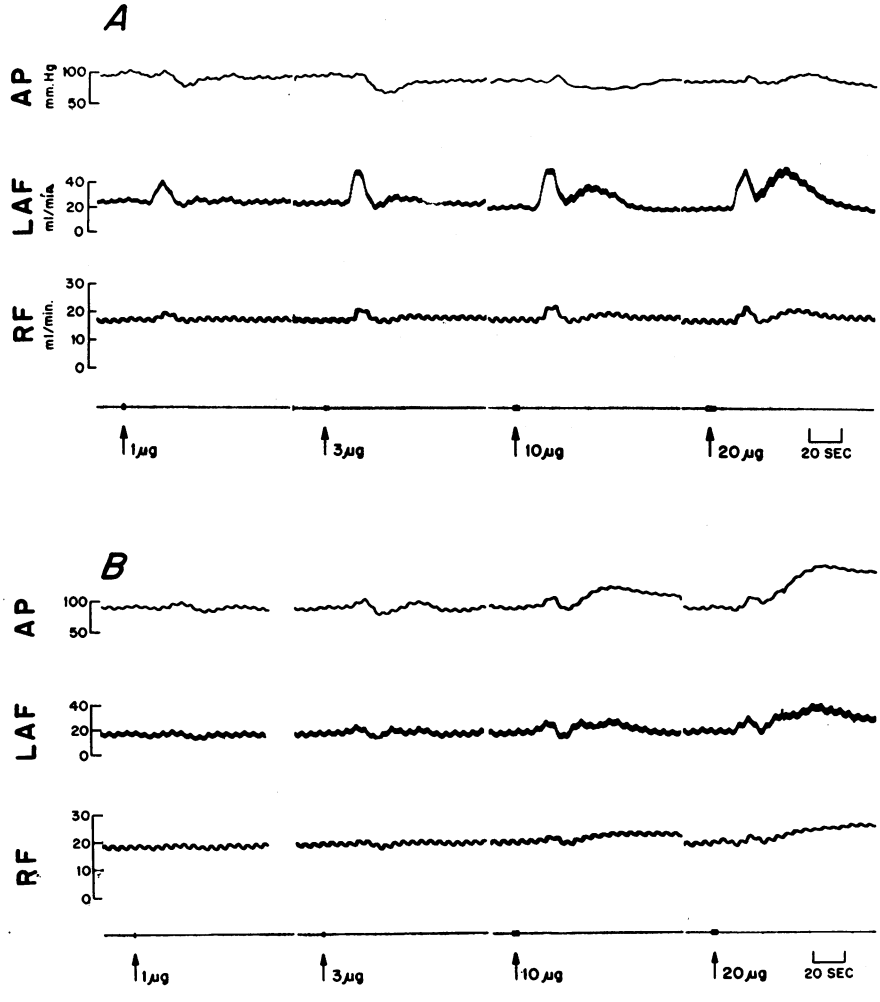

Fig. 5. Effects of increasing intravenous doses of adrenaline on mean flow in the right coronary (RF) and left anterior descending (LAF) coronary arteries and on aortic pressure (AP). Upper traces (*A*). Before beta-adrenergic blockade. Lower traces (*B*). After beta-adrenergic blockade with propranolol 1 mg/kg.

The increase in mean coronary flow was as great for adrenaline as for noradrenaline, although mean aortic pressure was often reduced by the former and always increased by the latter.

In some animals the effects of increasing the dose of adrenaline and noradrenaline over the range of 0.05 to 1 μg/kg were studied. The flow increase of Stage II became progressively more prominent as compared to that of Stage I (Fig. 5,*A*).

Although beta adrenergic blockade greatly potentiated the pressor effect of adrenaline and slightly increased that of noradrenaline the increase in coronary flow produced by these agents was much less than before blockade (Figs. 4, 5). The reduction of coronary vascular resistance was always less than before blockade and resistance actually increased in 5 out of 10 animals (Table 2). After blockade the shortening of systole and the increase in heart rate, peak aortic flow, stroke aortic flow and cardiac output previously produced by adrenaline and noradrenaline were abolished or reduced (Figs. 4, 5).

TABLE 2

MAXIMUM PERCENTAGE CHANGES IN CORONARY VASCULAR RESISTANCE DURING STAGE I ADRENERGIC RESPONSES PRODUCED BY INTRAVENOUS INJECTION OF 20 μG ADRENALINE AND NORADRENALINE BEFORE AND AFTER BETA-ADRENERGIC BLOCKADE IN 10 DOGS

" — " Indicates not tested

Before beta-adrenergic blockade		After beta-adrenergic blockade	
Adrenaline	Noradrenaline	Adrenaline	Noradrenaline
−17	−16	0	+56
−31	−39	− 5	−11
−11	−18	− 8	0
−50	−32	0	+14
−20	—	+11	—
−16	—	—	—
− 9	—	—	—
−38	—	+21	—
−18	−18	−13	−18
−20	−23	+44	+30

The changes in coronary vascular resistance before and after beta-adrenergic blockade are shown in Table 2.

DISCUSSION

Coronary flow during late diastole is determined by the aortic pressure and the vasomotor state of the coronary bed. A reduction in the ratio of aortic late diastolic pressure to late diastolic coronary flow indicates dilatation of the coronary resistance vessels (Green, Wegria & Boyer, 1942). In our experiments intracoronary injections of adrenaline and noradrenaline which were without effect on aortic pressure increased late diastolic coronary flow. These agents are therefore coronary vasodilators. The instantaneous flow pattern is not uniform during the vasodilator response. In the first few seconds both systolic and diastolic flow increase. We believe that adrenaline and noradrenaline exert a direct pharmacological effect on the coronary vessels during this period because (*a*) the response is very rapid and occurs at the same time (3–6 sec) as that following the injection of recognized coronary vaso-

dilators, e.g., glyceryl trinitrate ; (*b*) the dilator response begins at the same time as the constrictor response seen after beta-adrenergic blockade ; (*c*) the instantaneous flow pattern is identical to that produced by glyceryl trinitrate or by reactive hyperaemia (Ross, Kolin & Austin, 1964) ; (*d*) the response is not accompanied by changes attributable to myocardial stimulation. The instantaneous coronary flow pattern undergoes a striking change with the onset of the inotropic action of the catecholamines. Systolic flow is reduced and then reversed while diastolic flow continues to rise. At the same time the duration of left ventricular ejection is reduced and peak aortic flow is increased.

Adrenergic coronary vasoconstriction was not observed in our experiments except after beta-adrenergic blockade. In this respect our results differ from those of others who have claimed that vasoconstriction is the primary adrenergic response of the coronary vessels. Garcia-Ramos, Alanis & Luco (1950) reported that intracoronary adrenaline usually, although not invariably, produced a transient slight reduction of coronary flow in the isolated heart. Hardin, Scott & Haddy (1961) perfused at constant flow the coronary vessels of beating and fibrillating hearts performing no external work and used coronary pressure changes as an indication of variations in vascular resistance. They observed that intracoronary noradrenaline invariably produced an initial vasoconstriction while intracoronary adrenaline occasionally produced an initial vasodilatation but more often caused vasoconstriction. Berne (1958), using bristle flow meters or rotameters, found that in fibrillating, arrested and beating canine hearts intracoronary adrenaline or noradrenaline produced a transient vasoconstriction preceding a more prolonged vasodilatation. In the beating heart, the magnitude of the initial vasoconstriction was very small and the mean increase of resistance following 1 microgram adrenaline or noradrenaline was less than 4%. Berne attributed previous failures to demonstrate coronary vasoconstriction to various deficiencies in technique. However, Denison *et al.* (1956), using the square wave electromagnetic flowmeter and cannulating probes, observed only increases in flow following intracoronary adrenaline and noradrenaline. These authors did not divide the response into the two stages which we have described above, but they are clearly seen in their records.

Although the effects of intravenous catecholamines on the coronary vascular bed are difficult to assess owing to changes of heart rate, arterial pressure and cardiac output it is of interest that the same sequence of changes in the instantaneous coronary flow patterns occur after intravenous adrenaline and noradrenaline as when these agents are given by the intracoronary route. It is unlikely that our experimental method results in abnormal adrenergic responses since similar effects have been reported by Rayford, Khouri, Huvos & Gregg (1961) in conscious dogs following intravenous adrenaline. Using an electromagnetic method, they observed marked increases in both systolic and diastolic coronary flow without alteration of blood pressure or heart rate. Other workers who have obtained evidence for an intrinsic beta-adrenergic mechanism in the coronary vessels of the dog include Klocke, Kaiser, Ross & Braunwald (1965) and Zuberbuhler & Bohr (1965).

Intracoronary pronethalol and propranolol increase coronary flow in a manner identical to the Stage I increase produced by adrenaline and noradrenaline before beta-adrenergic blockade. In common with Black & Stephenson (1962) we have found no evidence of myocardial stimulation by pronethalol. Dornhorst & Robinson (1962) observed that

intrabrachial arterial injections of pronethalol in man produced vasodilatation in the arm. This effect cannot be due to beta-adrenergic blockade. The structural similarity between pronethalol, propranolol and isoproterenol suggests that the vasodilatation which they produce in the blood vessels of skeletal and cardiac muscle may be due to beta-adrenergic receptor stimulation.

There have been few studies of adrenergic responses following beta-adrenergic blockade. Hashimoto, Shigei, Imai, Saito, Yago, Uei & Clark (1960) used a bubble flow meter to measure coronary flow in a Langendorff preparation perfused by cross circulation from a donor dog. Intracoronary injections of adrenaline and noradrenaline produced an increase in coronary flow and myocardial oxygen consumption, but after beta-adrenergic blockade produced by dichloroisoproterenol the same drugs reduced coronary flow but did not significantly alter oxygen consumption. Our results are similar to those of Hashimoto *et al.* in that we have also observed that intracoronary adrenaline and noradrenaline initially produced coronary vasoconstriction after beta-adrenergic blockade. This vasoconstriction began after the same time interval as did the vasodilatation obtained prior to blockade and persisted even after the onset of myocardial stimulation shown by reduction in the duration of systole and reversal of systolic coronary flow. Hashimoto *et al.* considered that sympathomimetic amines produced coronary vasoconstriction, which was normally masked by the metabolic effects of myocardial stimulation but could be revealed by blocking the latter with dichloroisoproterenol. An equally possible interpretation and one more in keeping with our observations is that both alpha and beta receptors are present in the coronary vessels and that normally the beta response predominates. After beta blockade, alpha receptor stimulation results in coronary vasoconstriction. This hypothesis may explain the conflicting reports concerning the adrenergic mechanisms of the coronary vessels since different experimental approaches might favour either alpha- or beta-adrenergic stimulation.

SUMMARY

1. Gated sine-wave electromagnetic flow meters were used to study the effects of adrenaline and noradrenaline on blood flow in the unopened coronary arteries of anaesthetized open-chest dogs.

2. Intracoronary injection of these amines invariably increased coronary flow. During the first few sec following injection both systolic and diastolic flows increased. Evidence is presented which suggests that this initial increase is due to a primary pharmacological vasodilatation.

3. After beta-adrenergic blockade intracoronary adrenaline and noradrenaline produced coronary vasoconstriction.

4. These observations suggest that both alpha- and beta-adrenergic receptors are present in the coronary resistance vessels of the dog. In the anaesthetized open-chest animal beta-adrenergic responses predominate but alpha responses can be revealed by beta-adrenergic blockade.

The work was supported by grants USPHS HE03092 and USN Nonr 233(38).

REFERENCES

BERNE, R. M. (1958). Effect of epinephrine and norepinephrine on coronary circulation. *Circulation Res.*, **6**, 644–655.

BLACK, J. S. & STEPHENSON, J. S. (1962). The pharmacology of a new adrenergic beta-receptor-blocking compound (nethalide). *Lancet*, **ii**, 311–314.

COX, P., ARORA, H. & KOLIN, A. (1963). Electromagnetic determination of carotid blood flow in the anaesthetized rat. *I.E.E.E. Trans. Biomed. Electronics*, **10**, 171–173.

DENISON, A. B., Jr., BARDHANABAEDYA, S. & GREEN, H. D. (1956). Adrenergic drugs and blockade on coronary arterioles and myocardial contraction. *Circulation Res.*, **4**, 653–658.

DORNHORST, A. C. & ROBINSON, B. F. (1962). Clinical pharmacology of a beta-adrenergic blocking agent (nethalide). *Lancet*, **ii**, 314–316.

FEINBERG, H. & KATZ, L. N. (1958). Effect of catecholamines, l-epinephrine and l-norepinephrine on coronary flow and oxygen metabolism of the myocardium. *Amer. J. Physiol.*, **193**, 151–156.

GARCIA-RAMOS, J., ALANIS, J. & LUCO, J. (1950). Estudios sobre la circulation coronaria II. Las acciones del vago y del simpatico. *Arch. Inst. Cardiol. Mex.*, **20**, 534–550.

GREEN, H. D., WEGRIA, R. & BOYER, N. H. (1942). Effect of epinephrine and pitressin on coronary artery inflow in anesthetized dogs. *J. Pharmacol. exp. Ther.*, **76**, 378–391.

GREGG, D. E. & FISHER, L. C. (1963). Blood supply to the heart. In *Handbook of Physiology*. Section 2, *Circulation*, Vol. II, 1517–1584. Washington, D.C.: American Physiological Society.

GREGG, D. E., KHOURI, E. M. & RAYFORD, C. R. (1965). Systemic and coronary energetics in the resting unanesthetized dog. *Circulation Res.*, **16**, 102–113.

HARDIN, R. A., SCOTT, J. B. & HADDY, F. J. (1961). Effect of epinephrine and norepinephrine on coronary vascular resistance in dogs. *Amer. J. Physiol.*, **201**, 276–280.

HASHIMOTO, K., SHIGEI, T., IMAI, S., SAITO, Y., YAGO, N., UEI, I. & CLARK, R. E. (1960). Oxygen consumption and coronary vascular tone in the isolated fibrillating dog heart. *Amer. J. Physiol.*, **198**, 965–970.

KLOCKE, F. J., KAISER, G. A., ROSS, J., Jr. & BRAUNWALD, E. (1965). An intrinsic adrenergic vasodilator mechanism in the coronary vascular bed of the dog. *Circulation Res.*, **16**, 376–382.

KOLIN, A. & KADO, R. T. (1959). Miniaturization of the electromagnetic blood flow meter and its use for the recording of circulatory responses of conscious animals to sensory stimuli. *Proc. Nat. Acad. Sci..*, **45**, 1312–1321.

KOLIN, A., ROSS, G., GAAL, P. & AUSTIN, S. (1964). Simultaneous electromagnetic measurement of blood flow in the major coronary arteries. *Nature*, **203**, 148–150.

RAYFORD, C. R., KHOURI, E. M., HUVOS, A. & GREGG, D. E. (1961). Some determinants of coronary flow in intact dogs. *Physiologist*, **4**, 92.

ROSS, G., KOLIN, A. & AUSTIN, S. (1964). Electromagnetic observations of coronary blood flow. *Proc. Nat. Acad. Sci.*, **52**, 692–699.

ZUBERBUHLER, R. C. & BOHR, D. F. (1965). Responses of coronary smooth muscle to catecholamines *Circulation Res.*, **16**, 431–440.