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An analysis of the coronary vascular responses to catecholamines, using a modified Langendorff heart preparation

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Summary

1. A modified Langendorff heart preparation from the guinea-pig was used to analyse catecholamine responses. Contractile force, heart rate and coronary perfusion pressure were recorded.

2. Four components of the vascular response could be identified.

(*a*) The initial phase was a vasoconstriction mediated by α-adrenoceptors which preceded any effects on heart rate and force.

(*b*) A secondary constriction followed, which was due to the increased myocardial compression during positive inotropic and chronotropic responses.

(*c*) The third, more predominant, effect was a prolonged dilatation probably associated with the increased metabolic activity of the heart.

(*d*) A fourth component was a direct vasodilatation mediated by β-adrenoceptors which was evident when small doses of catecholamines were used but was usually masked by the more pronounced metabolically linked dilatation.

3. The actions of salbutamol were examined and since it caused direct vasodilatation by stimulation of β-adrenoceptors without other myocardial effects, these adrenoceptors were classified as the β_2-type.

4. I.C.I. 50,172 was employed to block selectively the myocardial effects due to stimulation of β_1-adrenoceptors and leave the vasodilator β_2-adrenoceptors unaffected.

5. Adrenaline, noradrenaline and isoprenaline were compared at two dose levels, in the presence or absence of effects on heart rate and force.

6. Constrictor or dilator effects were found in the absence of other effects and were shown to depend to some extent on the rate of coronary perfusion.

Introduction

The overall effect of catecholamines on the coronary circulation is vasodilatation (Wégria, 1951 ; Charlier, 1961 ; Parratt, 1968). This response frequently accompanies positive inotropic and chronotropic effects and is attributed to a metabolic change resulting from the increased work of the heart (Berne, 1964 ; Parratt, 1967).

It is not surprising, therefore, that β-adrenoceptor blockade of the cardiac effects should also abolish the vasodilator response (Hashimoto, Shigei, Imai, Saito, Yago, Uei & Clark, 1960 ; Siegal, Gilmore & Sarnoff, 1961). A coronary vasodilatation to adrenaline, noradrenaline and isoprenaline has, however, been observed in the absence of any other myocardial effects in intact anaesthetized animals (Eckenhoff, Hafkenschiel & Landmesser, 1947 ; Denison, Bardhanabaedya & Green, 1956 ; Gaal, Kattus, Kolin & Ross, 1966), in conscious animals (Pitt, Elliott & Gregg, 1966), and in the potassium arrested isolated heart where no increases in force and rate are possible (Klocke, Kaiser, Ross & Braunwald, 1965). These responses, like the increases in heart rate and force, are blocked by β-adrenoceptor antagonists (Doutheil, Bruggencate & Kramer, 1964 ; Klocke *et al.*, 1965 ; Doutheil, 1966), and in some cases are reversed to reveal a constriction (Parratt, 1965 ; Gaal *et al.*, 1966 ; Pitt *et al.*, 1966). This raises the possibility that direct constriction of the coronary vessels can occur, and indeed this response alone has been recorded following the administration of adrenaline and noradrenaline to isolated (Garcia-Ramos, Alanis & Luco, 1950 ; Berne, 1958 ; Hardin, Scott & Haddy, 1961) and intact hearts (Brandfonbrener, Gracey, Nice & Haddy, 1962 ; Kaverina, 1965).

The present analysis of the multiple responses of the coronary circulation to catecholamines has been facilitated by the identification of all these phases in a single preparation. A further aid has been the use of selective agents which act at β_1- and β_2-adrenoceptors (Lands, Arnold, McAuliff, Luduena & Brown, 1967), in an attempt to separate the cardiac (β_1) and coronary vascular effects and to assign a receptor type to the latter.

Methods

Guinea-pigs of either sex and weight range 150–400 g were killed by a blow on the head. The hearts were immediately removed and a glass cannula tied into the cut aorta, for retrograde perfusion of the coronary vessels by the method of Langendorff (1895). This was performed within 2 min to avoid intracoronary thrombus formation.

A constant rate of perfusion, as employed by others (Katz, Paine & Tiller, 1939 ; Larsen, 1948 ; Luduena, Miller & Wilt, 1955), was produced within the range 5–7 ml/min by a Watson-Marlow flow inducer. The Krebs-bicarbonate solution (composition in g/l. distilled water: NaCl, 6·92 ; KCl, 0·345 ; $CaCl_2 2H_2O$, 0·28 ; $NaHCO_3$, 2·1 ; $MgSO_4 7H_2O$, 0·29 ; glucose, 2·0 ; $NaH_2PO_4 2H_2O$, 0·16) was gassed with 5% CO_2 in oxygen before entering the flow inducer, after which it was passed through a warming coil (37° C) at the base of which was the aortic cannula. Situated between the flow inducer and the warming coil was a pressure transducer (Consolidated Electrodynamics Type 4-327-L221) which recorded alterations in perfusion pressure [resting level between 25 and 50 mmHg (1 mmHg$\equiv$1.33 mbar)] arising from changes in coronary vascular resistance on a Devices M4 polygraph. A Condon manometer was also introduced into the system, between the flow inducer and cannulated aorta at the level of the pressure transducer. This was to accommodate some degree of volume change during drug responses. The final system was able to detect small transient changes in the coronary vascular resistance.

Isometric contractions of the heart were recorded with a transducer (Ether, Type UFl, 57 g sensitivity range) attached via a pulley to a heart clip on the apex of the

ventricles. The signal produced was used to trigger a Nielson instantaneous rate-meter which was connected to a third channel of the polygraph to provide a continuous record of heart rate.

Drugs were injected directly into the connecting rubber tubing immediately before entry into the warming coil. The volume administered was between 0·025 and 0·2 ml and this produced an injection artefact which was well separated from the drug response. Antagonists were usually added to a Ringer solution reservoir.

Drugs used were: adrenaline acid tartrate (B.D.H. Ltd.), I.C.I. 50,172 (4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide) (I.C.I. Ltd.), isoprenaline sulphate (B.D.H. Ltd.), L-noradrenaline bitartrate (Koch-Light Laboratories), propranolol (I.C.I. Ltd.), phentolamine mesylate (Rogitine, CIBA), salbutamol (Allen & Hanburys Ltd.). All solutions were freshly prepared in 0·9% w/v sodium chloride solution. Amounts referred to in the text are expressed as the base.

Results

Figure 1 illustrates a typical response to a dose of adrenaline which increases the force and rate of cardiac contractions. The dose is repeated at a faster chart speed to demonstrate more clearly that there are three well defined phases in the response of the coronary circulation. These are: (*a*) an initial rise in perfusion pressure which precedes any effects on the force and rate of heart beat; (*b*) a secondary rise in pressure which occurs simultaneously with the onset of positive inotropic and chronotropic responses. At this point the excursions of the pen either side of the mean pressure were more exaggerated; (*c*) a fall in perfusion pressure which often

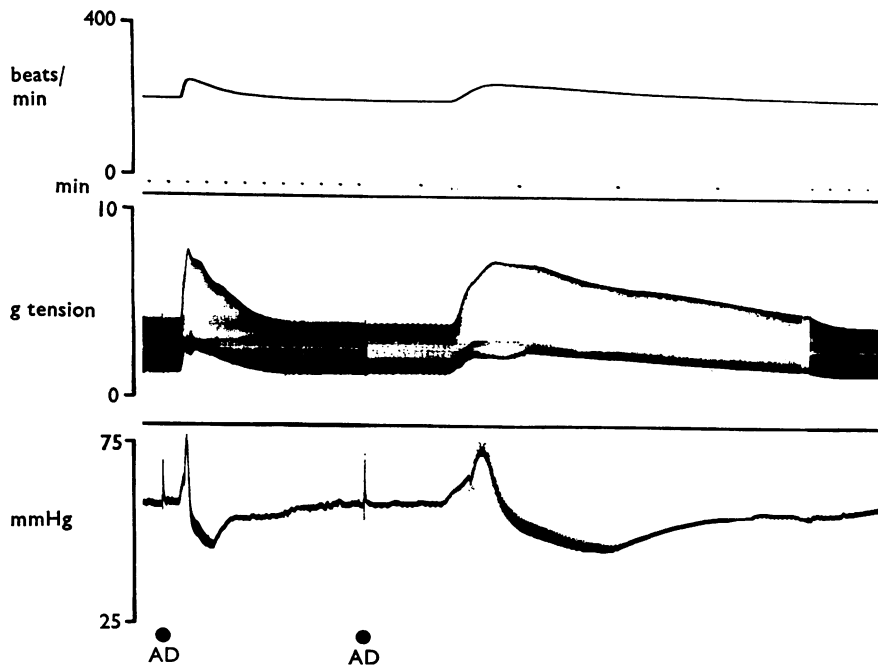

FIG. 1. Guinea-pig isolated perfused heart. The effects of adrenaline on the heart rate (upper record), contractile force (middle record) and coronary perfusion pressure (lower record). The same dose (0·1 μg) of adrenaline (AD) was administered at two different chart speeds.

occurs while the heart is still excited, but continues well after the force and rate have returned to normal. There is a gradual return to the resting pressure.

These three phases did not, however, appear at all dose levels used, as shown in Fig. 2, where a dose range starting from a threshold level was used. Doses of adrenaline that were without effect on heart rate and force produced an increase in coronary resistance. A similar pressure increase also occurred with small positive inotropic and chronotropic responses, and it was not until more noticeable myocardial responses were produced that the triphasic adrenaline response on the coronary circulation was evident.

At all doses there was an initial constrictor phase. This was abolished by the α-adrenoceptor blocking agent phentolamine (0·2 μg/ml), leaving at the higher adrenaline doses, a rise in pressure characterized by forceful and more pronounced excursions of the recorder stylus. This was superimposed on the overall dilatation and coincided with the positive inotropic and chronotropic responses. Both these vascular responses were removed when the myocardial effects were blocked by the further introduction of propranolol (0·05 μg/ml) to the perfusion fluid (Fig. 2C).

When the order of adding these antagonists was reversed (Fig. 3), initial β-adrenoceptor blockade removed the myocardial effects of adrenaline together with the coronary vasodilatation. The remaining rise in perfusion pressure was not accompanied by forceful excursion of the stylus but was susceptible to α-adrenoceptor blockade, suggesting that it was equivalent to the first component of the control adrenaline response.

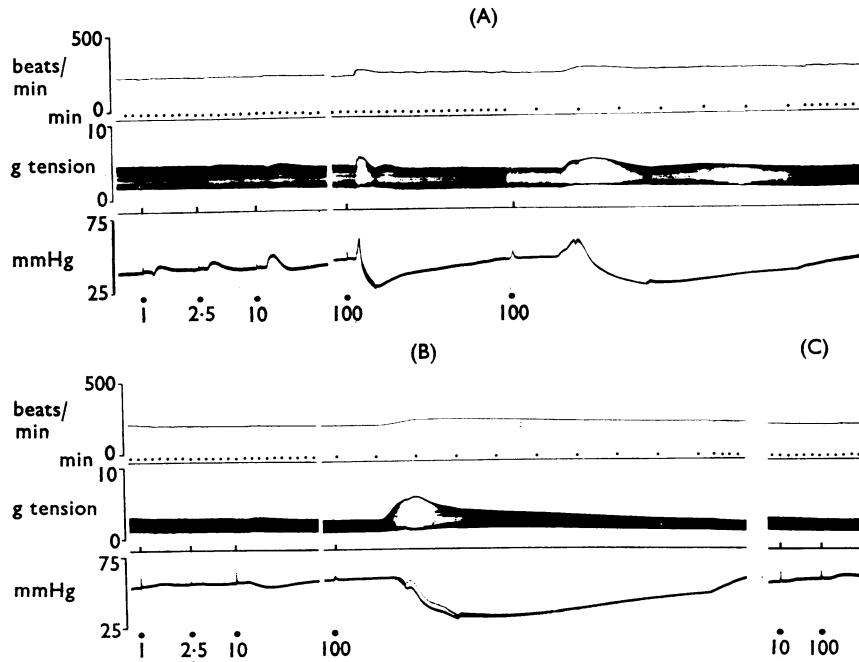

FIG. 2. Guinea-pig isolated perfused heart. A, Effects of increasing doses (ng) of adrenaline (●) on heart rate (upper record), contractile force (middle record) and coronary perfusion pressure (lower record). The 100 ng dose of adrenaline was repeated at a faster chart speed. B, Effect on these adrenaline responses of phentolamine (0·3 μg/ml) added to the perfusion solution. C, Effects of both phentolamine (0·3 μg/ml) and propranolol (0·1 μg/ml) on the adrenaline responses.

Unlike adrenaline, salbutamol was found consistently to produce falls in pressure which in smaller doses (5–25 ng) were without effects on the force and rate of cardiac contractions. The selectivity for the coronary vessels was however not as marked as might be expected. The β_1-adrenoceptor effects on the rate and force could quite easily be observed with doses (100 ng) only slightly in excess of those producing only dilatation. The dilatation was antagonized by propranolol (Fig. 4). It was not, however, affected by I.C.I. 50,172 in a concentration (0·3 μg/ml) that inhibited the β_1 cardiac effects of isoprenaline (Fig. 5). Like salbutamol, I.C.I. 50,172 was not as

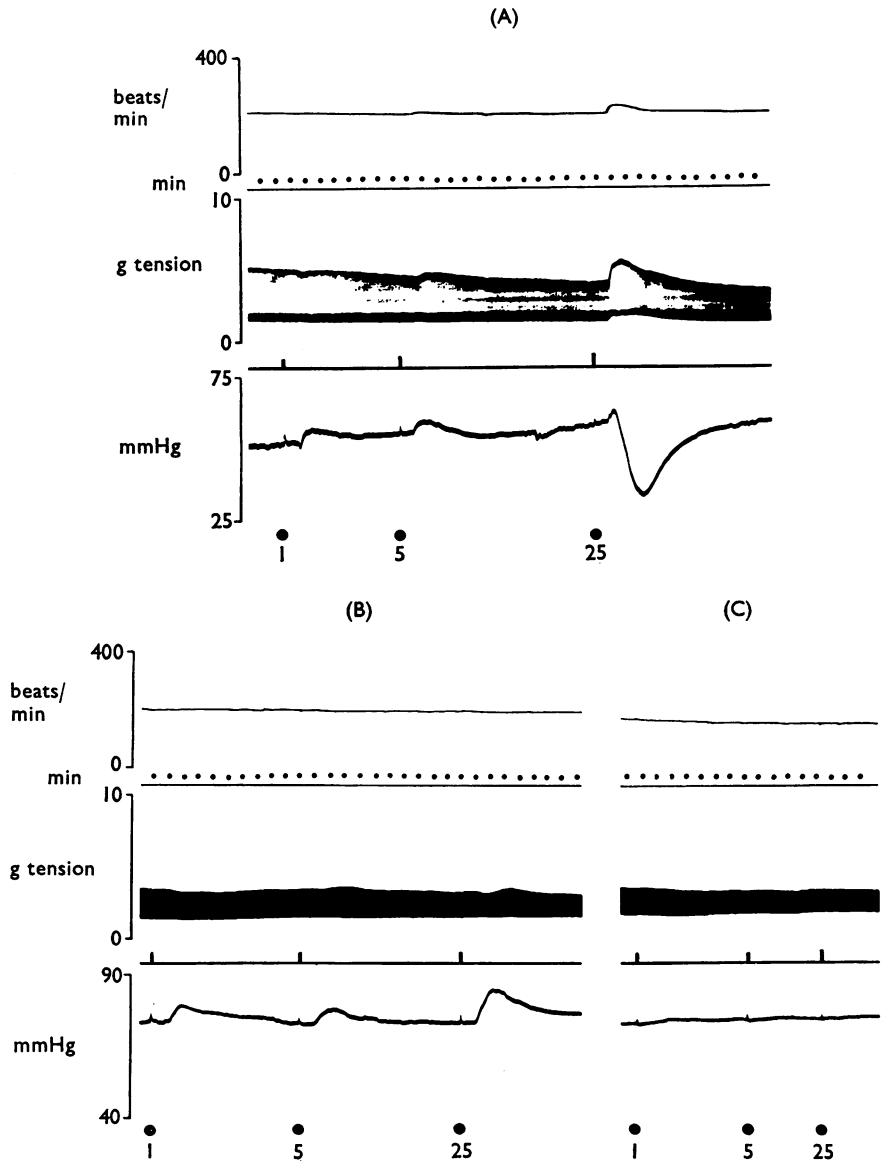

FIG. 3. Guinea-pig isolated perfused heart. The effects of propranolol (0·05 μg/ml) added to the perfusion solution in B and C and phentolamine (0·2 μg/ml) in C, on responses of heart rate (upper record), contractile force (middle record) and coronary perfusion pressure (lower record) to increasing doses (ng) of adrenaline (●).

selective as might be anticipated, since only slightly larger concentrations (0·5 μg/ml) did inhibit the dilatation. Following blockade by I.C.I. 50,172, isoprenaline also caused a small dilatation but now without the positive inotropic and chronotropic effects.

Therefore a fourth dilator component of the coronary vascular response can now be identified. This vasodilatation apparently contributes to the much larger fall in pressure that coincides with the increases in heart force and rate, but is usually masked by it.

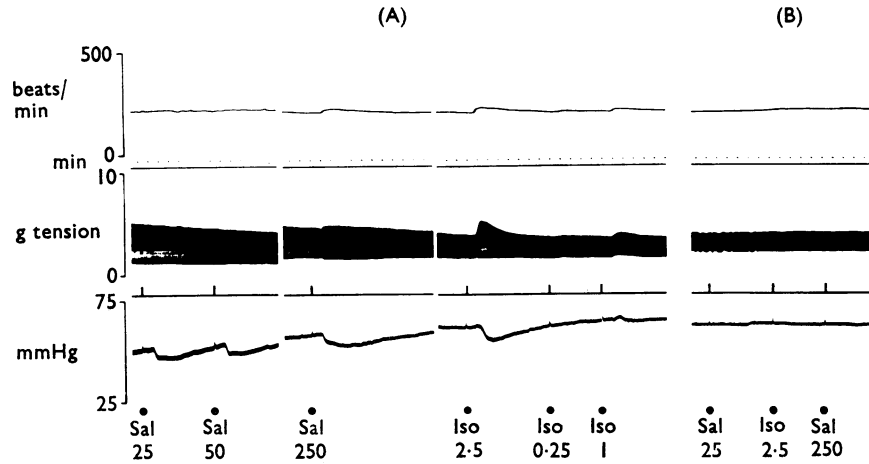

FIG. 4. Guinea-pig isolated perfused heart. The effect of propranolol (0·05 μg/ml) on the responses of heart rate (upper record), contractile force (middle record) and coronary perfusion pressure (lower record) to salbutamol (Sal) and isoprenaline (Iso). Propranolol was added to the perfusion solution between A and B. Doses are in nanogrammes.

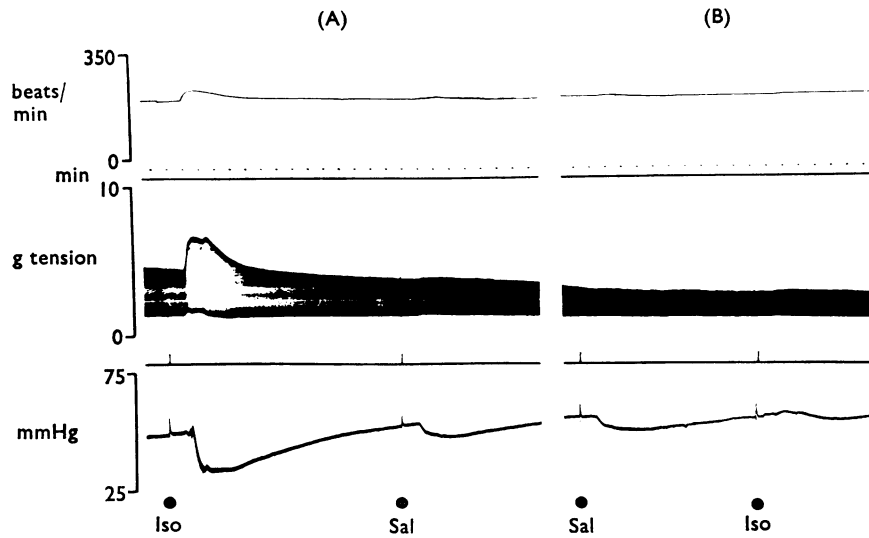

FIG. 5. Guinea-pig isolated perfused heart. The effect of I.C.I. 50,172 (0·3 μg/ml) on the responses of heart rate (upper record), contractile force (middle record) and coronary perfusion pressure (lower record) to isoprenaline, 5 ng (Iso) and salbutamol, 25 ng (Sal). I.C.I. 50,172 was added to the perfusion solution between A and B.

The responses to adrenaline were next compared with those to noradrenaline and isoprenaline. Two dose levels were used. The higher doses were selected to affect all three parameters and produce the complete pressure response while the lower doses influenced only the perfusion pressure without effects on the rate and force of myocardial contractions. Adrenaline and noradrenaline were quantitatively and qualitatively similar on all parameters examined, although noradrenaline was often more potent than adrenaline in increasing the force, but weaker in increasing the rate of contractions (Fig. 6). Generally the size of the overall depressor component followed this difference in inotropic response, the greater fall in pressure being produced by the drug exhibiting the larger inotropic effect. Isoprenaline, at only 1/10 the dose of the other catecholamines, produced qualitatively similar responses. Figure 6 shows that there is a greater dilatation due to isoprenaline which is associated with a similar force increase to adrenaline and noradrenaline but a larger rate increase. The initial rise in pressure was greatest with noradrenaline and least with isoprenaline. During propranolol infusion (0·05 μg/ml), there remained only constrictor responses to adrenaline and noradrenaline, the former being more active in this respect. Subsequent perfusion with phentolamine (0·2 μg/ml) blocked these rises in pressure.

When threshold doses of these catecholamines were examined in more detail, conflicting results were obtained. Doses that produced no effects on heart rate and force were used so that myocardial effects on the coronary circulation could be excluded. Adrenaline had so far been observed to produce predominantly a vasoconstriction mediated by α-adrenoceptors. After further work however it was found that in a few hearts a pure dilatation or even a biphasic response was obtained (Fig. 7). Reference to Fig. 3 in fact reveals a very slight initial fall in pressure to the smallest dose of adrenaline and this was not present during the propranolol infusion. The type of response to adrenaline in any one heart was always mimicked by noradrenaline but not necessarily by isoprenaline. When adrenaline constricted so did noradrenaline, but to a lesser extent (Fig. 7A). Isoprenaline in a few hearts also constricted coronary vessels at doses where positive inotropic responses were just

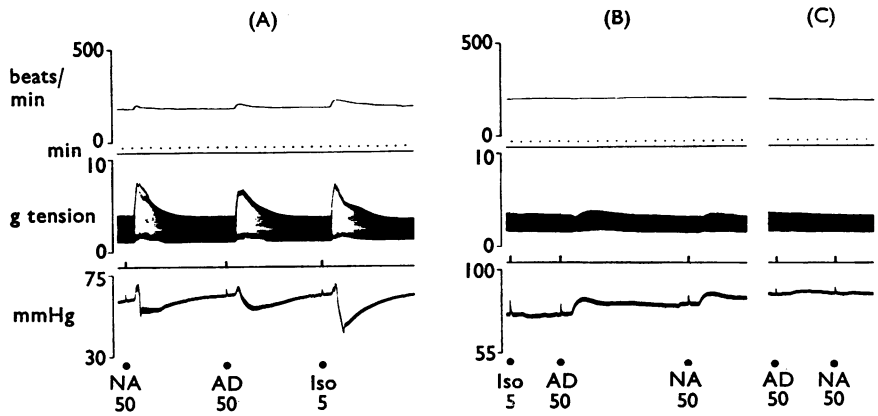

FIG. 6. Guinea-pig isolated perfused heart. The effects of noradrenaline (NA), adrenaline (AD) and isoprenaline (Iso) in doses (ng) which produce responses of the heart rate (upper record), contractile force (middle record) and coronary perfusion pressure (lower record). Between A and B, propranolol (0·05 μg/ml) and between B and C both propranolol (0·05 μg/ml) and phentolamine (0·2 μg/ml) were introduced to the perfusion solution.

evident. Hearts exhibiting a dilatation to adrenaline (Fig. 7B) also gave this same response to noradrenaline and isoprenaline, the order of potency being isoprenaline>adrenaline>noradrenaline. Biphasic responses to isoprenaline did not occur, but adrenaline and noradrenaline produced them in the same hearts, while isoprenaline usually dilated the coronary vessels (Fig. 7C).

A possible explanation of this difference came from experiments in which a dilator response to adrenaline or noradrenaline could be converted to a biphasic response immediately following an increase in the rate of perfusion (Fig. 8). The perfusion rate for any one heart would be arrived at arbitrarily at the beginning of the experiment over a fairly narrow range (5–7 ml/min) to suit that heart from the point of view of optimum contractile force and absence of arrhythmias. It would appear that, to a certain extent, the flow rate influences the type of response to small threshold doses of adrenaline and noradrenaline. The results of thirty-five experiments showed that when threshold doses of adrenaline produced a rise in pressure, the mean resting pressure was $57{\cdot}1 \pm 2{\cdot}4$ mmHg ($n=24$), compared with a value of $45{\cdot}4 \pm 3{\cdot}1$ mmHg ($n=11$) when depressor responses occurred.

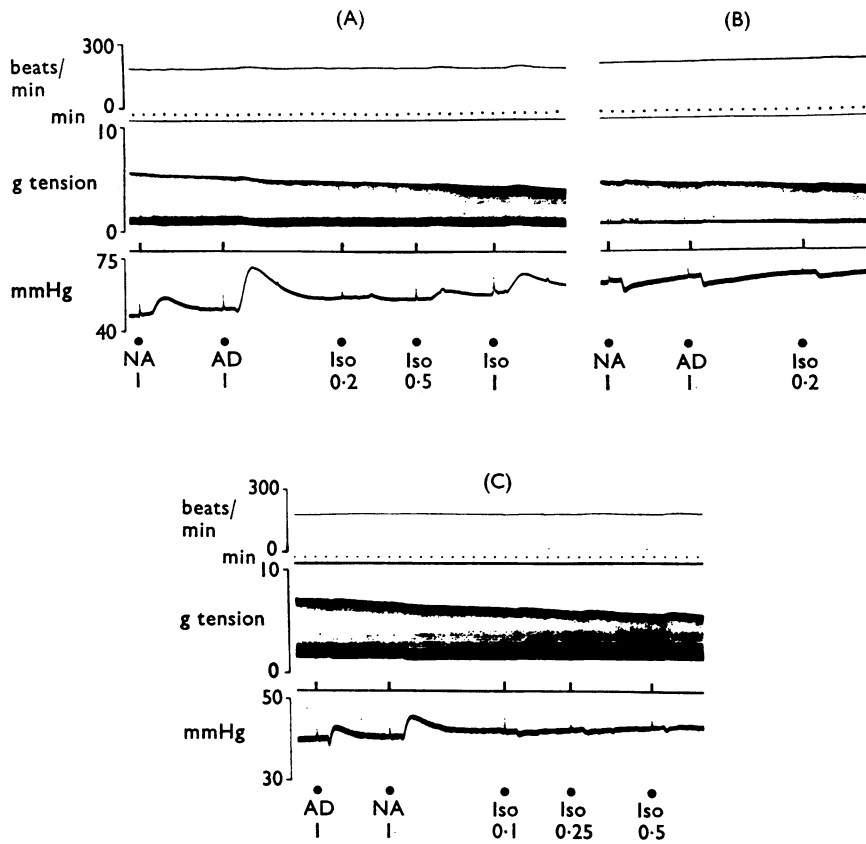

FIG. 7. Guinea-pig isolated perfused hearts. The contrasting effects of adrenaline (AD), noradrenaline (NA) and isoprenaline (Iso) on the coronary perfusion pressure (lower record) in doses (ng) that had no effect on heart rate (upper record) or contractile force (middle record). Panels A, B and C were obtained from three different preparations.

Discussion

The coronary vascular response to doses of catecholamines that produce positive inotropic and chronotropic effects on guinea-pig hearts could be divided into three clear stages. These occurred in a consistent chronological order. Initially a constriction preceded the effects on the heart rate and force; this was followed by a secondary rise in perfusion pressure during which there was a greater excursion of the trace either side of the mean pressure. Finally there was a prolonged fall in pressure which outlasted the myocardial effects.

The first phase of the response was a direct action on the coronary blood vessels due to vasoconstriction mediated by α-adrenoceptors, because it may be abolished by the α-adrenoceptor antagonist phentolamine. This response alone was produced by threshold doses of adrenaline which had no other observable effects on the heart, and this too was susceptible to α-adrenoceptor blockade. Noradrenaline produced a similar constriction but was less active. Kaverina (1965) and Saito (1959) have also observed a constrictor response to adrenaline which was blocked by dihydroergotamine and phentolamine respectively. In the present investigation, however, after phentolamine a constrictor component remained with the larger doses. This was superimposed on the overall dilatation but accompanied the force and rate increases. Elimination of the latter effects by propranolol also abolished the secondary rise in perfusion pressure, along with the prolonged dilatation. They therefore appear to be closely related.

The effects of tachycardia and contractile force on the coronary circulation have been widely investigated and there has been some disagreement among workers in

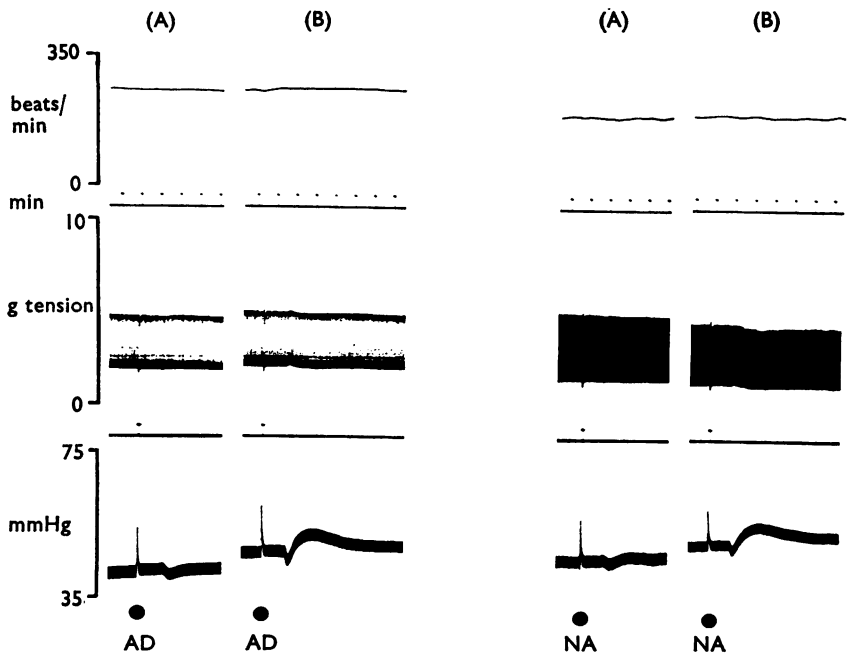

FIG. 8. Guinea-pig isolated perfused hearts. The effect of raising the perfusion rate between A and B on the coronary perfusion responses (lower record) to adrenaline (AD) and noradrenaline (NA). The results are from two different preparations and the doses used (1 ng) failed to influence heart rate (upper record) or contractile force (middle record).

this field. Wiggers (1954) claimed that cardiac systole augments coronary flow, but it is more widely believed that during systole, flow is restricted (Gregg & Green, 1940 a, b ; Sabiston & Gregg, 1957). Therefore during a positive inotropic response to adrenaline a greater resistance to flow can be expected due to increased compression on the coronary vessels by the myocardium (Melville & Lu, 1950 ; Douglas, Armengol & Talesnik, 1960). The tachycardia produced by adrenaline may also cause an impaired flow because under these conditions there is relatively more time in systole (Anrep & Häusler, 1929). Wiggers (1954) would again contradict this view, claiming that tachycardia increases coronary flow by a massaging effect. Furthermore, tachycardia in the intact heart also improves the coronary flow because of an increased cardiac output (Wégria, Frank, Wang & Lammerant, 1958 ; Lewis, Coffman & Gregg, 1961).

Catecholamines therefore appear to cause an initial resistance to coronary perfusion, firstly by a direct vasoconstriction mediated by α-adrenoceptors and secondly due to extravascular compression during the rate and force increases.

The fall in perfusion pressure which follows is longer lasting and is recognized as the predominant coronary effect of catecholamines *in vivo* and *in vitro* (Wégria, 1951 ; Charlier, 1961 ; Parratt, 1967, 1968). It has perhaps been the most difficult to interpret, but is generally accepted to be a result of the increased metabolic activity of the myocardium (Green, Wégria & Boyer, 1942 ; Melville & Lu, 1950 ; Douglas *et al.*, 1960 ; Hashimoto *et al.*, 1960 ; Hardin *et al.*, 1961 ; Siegal *et al.*, 1961 ; Berne, 1964). Metabolic inhibitors such as cyanide (Garcia-Ramos *et al.*, 1950) and fluoracetate (Saito, 1959) have been shown to inhibit the adrenaline induced dilatation in isolated hearts. It has been suggested that the increased cardiac activity releases vasodilator substances, examples of which include potassium ions (Dawes, 1941 ; Driscol & Berne, 1957), lactic acid (Mohme-Lundholme, 1957) and polypeptides such as bradykinin (Parratt, 1964 ; Lochner & Parratt, 1966). Also arising from increased myocardial activity will be a relative anoxia (Berne, 1958) which increases coronary flow (Green & Wégria, 1942 ; Wiggers, 1954 ; Berne, Blackmon & Gardner, 1957 ; Guz, Kurland & Freedberg, 1960 ; Feinberg, Katz & Boyd, 1962) and a suggested mechanism for this is the release of adenosine by the anoxia (Berne, 1964 ; Rubio & Berne, 1969). In the present work, the magnitude of the overall dilatation appeared related to the size of the positive inotropic and chronotropic responses. It was only evident when these were clearly defined and the tension developed was about doubled. This investigation confirms that the guinea-pig isolated heart is approximately equally sensitive to adrenaline and noradrenaline (Leusen & Essex, 1953), the latter occasionally produced a slightly greater force increase and when this was so, it also produced the greater dilator response. Whether increases in rate or in force are more important in controlling the dilatation was difficult to determine. Where rate increases were approximately equal, a larger force increase resulted in a greater dilatation, suggesting that force increases have more metabolic effect. Only 1/10 the dose of isoprenaline was required to produce a response identical to those of the larger doses of adrenaline and noradrenaline.

Previous attempts to separate the metabolically linked vasodilation from any direct coronary dilatation have proved difficult. As found in the present investigation, dilator responses to adrenaline, noradrenaline and isoprenaline can be observed in threshold doses without apparent myocardial effects. The order of potency was isoprenaline>adrenaline>noradrenaline. These responses have been recorded in

intact hearts as end-diastolic dilatation (Denison *et al.*, 1956) and as overall flow increases without other effects (Eckenhoff *et al.*, 1947 ; Gaal *et al.*, 1966 ; Pitt *et al.*, 1966).

Salbutamol is a selective stimulant of β_2-adrenoceptors which causes vasodilatation and bronchodilatation (Cullum, Farmer, Jack & Levy, 1969). It has weak effects on the β_1-adrenoceptors of the heart. I.C.I. 50,172 however is a selective antagonist of these β_1-adrenoceptors (Dunlop & Shanks, 1968). A combination of these agents in the present work has permitted a separation of the myocardial and coronary vascular effects of catecholamines. Small doses of salbutamol consistently caused coronary vasodilatation without positive inotropic or chronotropic effects, although larger doses did produce responses on all three parameters. These responses were antagonized by propranolol and it is concluded that there are β-adrenoceptors (dilator) in the coronary circulation. Furthermore, these adrenoceptors can now be classified as the β_2 type. Blockade of β_1-adrenoceptors by I.C.I. 50,172 eliminated the force and rate increases due to isoprenaline but left a direct dilatation and the dilatation to salbutamol unaltered. These selective β-adrenoceptor stimulants therefore provide a means of separating the metabolic and direct coronary dilatations to catecholamines. Parratt & Wadsworth (1969) have recently communicated to the British Pharmacological Society the results of experiments using I.C.I. 50,172 from which they conclude that isoprenaline increases coronary blood flow by the metabolic release of a vasoactive substance which has no effect on β_2 vascular adrenoceptors.

In the present analysis, the existence of both α- and β- (of the β_2 type) adrenoceptors could be demonstrated, and indeed direct constriction or dilatation to catecholamines was found at threshold doses which did not affect heart force and rate. The variability of this result, that is, whether constriction or dilatation occurred in individual hearts, was affected by the level of the resting perfusion pressure. Generally, dilator responses were associated with lower pressures and these could be converted to biphasic or solely constrictor responses by raising the rate and hence to some extent the pressure of perfusion. This is understandable since higher perfusion rates will distend the coronary vessels thus limiting any further drug induced dilatation and only constriction remains possible. Furthermore, as the experiment progresses at elevated pressures leakage of perfusion fluid into the extravascular intercellular spaces occurs (Larsen, 1948) forming an additional resistance to vascular relaxation. Most workers have demonstrated only direct constrictor responses in isolated hearts (Parratt, 1968) ; both were observed here, often in the same preparation. Which response predominates depends on the vascular resistance characteristics of individual hearts, of which the flow rate plays an important part. It is also possible that the coronary resistance lies at different levels of the vascular bed. In some hearts the smaller, more distal vessels which are endowed with a greater proportion of dilator β-adrenoceptors (Zuberbuhler & Bohr, 1965) may provide the resistance and a fall in pressure follows the administration of adrenaline. On raising the perfusion pressure, the resistance may now be offered by the larger proximal vessels containing mainly constrictor α-adrenoceptors. Finally, hearts will doubtless vary in their relative sensitivities to α- and β-adrenoceptor agonists which will also influence the nature and magnitude of the final vascular response.

These direct effects on the coronary vasculature, however, play only a minor role in the responses to larger doses of catecholamines since they are normally masked

by the more powerful effects of extravascular compression and metabolic dilatation due to the increased activity of the heart.

I would like to thank Dr. J. J. Armstrong of I.C.I. Ltd. for the generous gifts of propranolol and I.C.I. 50,172, and Dr. I. L. S. Mitchell of Allen & Hanburys Ltd. for the gift of salbutamol. I am also grateful to Christine Brown for assistance in preparing the figures.

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