

The effect of catecholamine infusions on myocardial blood flow, metabolic heat production and on general haemodynamics, before and after alprenolol (H56/28), in anaesthetized cats

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Summary

1. In cats anaesthetized with pentobarbitone sodium, infusions of adrenaline, noradrenaline ($0.5 \mu\text{g/kg}$ per min) and isoprenaline ($0.25 \mu\text{g/kg}$ per min) increased myocardial blood flow, myocardial heat production, left ventricular systolic and end-diastolic pressures, left ventricular +ve and -ve dp/dt max, and calculated cardiac output, effort and oxygen consumption. These effects (apart from the effect of noradrenaline on left ventricular systolic pressure) were markedly reduced by previous administration of alprenolol (0.5 or 1.0 mg/kg).
2. Infusions of adrenaline and noradrenaline increased arterial diastolic blood pressure and isoprenaline reduced it. After alprenolol the effects of adrenaline and noradrenaline were potentiated and that of isoprenaline abolished; in some experiments isoprenaline increased arterial diastolic pressure after alprenolol. Alprenolol did not influence the increases in arterial systolic pressure which followed the administration of adrenaline and noradrenaline.
3. Isoprenaline-induced tachycardia was markedly reduced and adrenaline tachycardia was converted to bradycardia after alprenolol. The bradycardia which occurred during noradrenaline infusions was unaffected.
4. After blockade by alprenolol, recovery of the effects of isoprenaline on left ventricular dp/dt and on heart rate occurred more quickly than recovery of the effects on arterial diastolic pressure. This suggests that alprenolol has a greater affinity for β_2 - than for β_1 -adrenoceptors.
5. Intravenous administration of acetylcholine decreased arterial blood pressure, left ventricular pressure and +ve and -ve dp/dt max. During recovery from these effects there was a marked increase in +ve dp/dt max, which was absent after the administration of alprenolol (0.5 mg/kg). Because this dose of alprenolol is thus able to block the effects of reflex sympathetic cardiac nerve stimulation but does not completely antagonize the effects of exogenous adrenaline on dp/dt , it is suggested that alprenolol may have some adrenergic neurone blocking activity.
6. Increases in liver and myocardial blood flow and heat production produced by noradrenaline, adrenaline and isoprenaline were reduced after alprenolol.
7. Isoprenaline reduced air-way resistance and this effect was abolished by alprenolol; increases in air-way resistance produced by adrenaline and noradrenaline were augmented. All three amines inhibited intestinal smooth

muscle contractions *in vivo*. Only the effect of isoprenaline was reduced by alprenolol.

Introduction

In a previous publication (Parratt & Wadsworth, 1969) the cardiovascular actions of the β -adrenoceptor blocking drug alprenolol (H56/28) were described and the conclusion drawn that it possessed pharmacological properties which would make it a useful anti-anginal agent. There is evidence for increased sympathetic transmitter release in angina (Parratt, 1970) so it was decided to assess how alprenolol modified the effects of catecholamine infusions with particular reference to their action on simultaneously measured myocardial blood flow, myocardial metabolic heat production, contractility and cardiac output.

Methods

Myocardial blood flow and heat production were measured in twenty-two cats using the heated thermocouple technique of Grayson (Grayson & Mendel, 1961; Grayson & Parratt, 1966). The cats were anaesthetized with pentobarbitone sodium (30 mg/kg). Left ventricular systolic and end-diastolic pressures (LVSP; LVEDP), left ventricular dp/dt , heart rate, femoral arterial pressure, right atrial pressure and the electrocardiogram were recorded as previously outlined (McInnes & Parratt, 1969) on an eight channel Elema-Schönander recorder (Mingograph 81). In two of the animals cardiac output was estimated by the pressure-time derivative method described by Greenfield, Patel, Barnett & Fox (1962). The femoral artery catheter was positioned in the descending aorta and the rate of change of the aortic pulse was continuously determined with a similar differentiating circuit to that used to measure left ventricular dp/dt . In the remaining experiments, cardiac output was assessed from the product of the heart rate and the pulse pressure assuming that arterial distensibility remained constant in each animal. The "cardiac effort index" was calculated from the product of the heart rate and the arterial (or left ventricular) systolic pressure (see Feinberg, Katz & Boyd, 1962). Liver blood flow and metabolic heat production were measured using heated thermocouples and intestinal motility and airway resistance by methods described in a previous paper (Parratt & Wadsworth, 1969). Blood pressure was measured in mm Hg (1 mm Hg \equiv 1.333 mbar).

Intravenous infusions of adrenaline (0.25–1.0 μ g/kg per min as base), nor-adrenaline (0.25–1.0 μ g/kg per min as base) and isoprenaline (0.1–0.5 μ g/kg per min as base) were given for a period of 5–10 min (usually 7 min) by means of a Sage slow injection pump. Infusions were given before, and at various times after, intravenous injections of alprenolol (0.5 or 1.0 mg/kg). The initial doses of catecholamines were chosen as being those that gave an increase in myocardial blood flow of at least 25% and were usually 0.25 μ g/kg per min (isoprenaline) and 0.5 μ g/kg per min (adrenaline and noradrenaline). Resting heart rate, arterial and left ventricular pressures and dp/dt were measured before each infusion, and a continuous record taken during and immediately after it; from the record the mean value of each parameter during the "steady state" period of the infusion was estimated.

In two experiments the effects of alprenolol on the myocardial responses to intravenous injections of acetylcholine (0.25 and $0.5 \mu\text{g/kg}$) were studied. There is a reflex increase in dp/dt during recovery from the depressor response to acetylcholine and this was used as a test to determine the extent of blockade, by alprenolol, of the effects of reflex sympathetic nerve activity.

Results

General haemodynamic effects

Typical responses to infusions of isoprenaline and adrenaline are shown in Figs. 1 and 2. Each figure shows the initial part of the infusion period before, and up

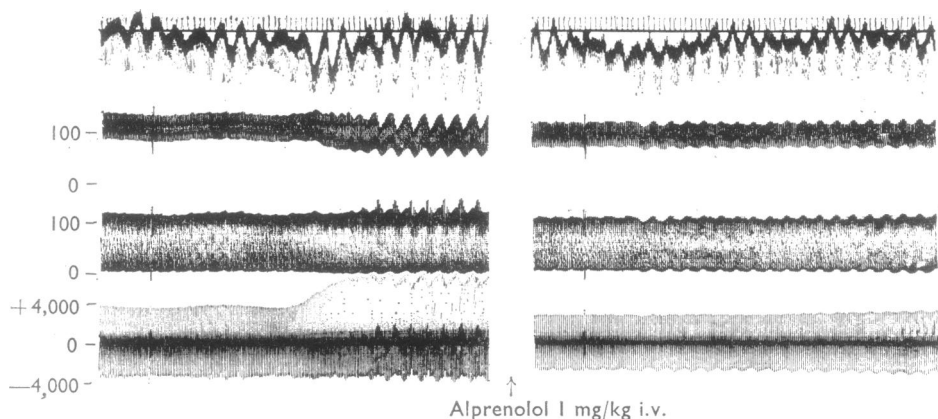


FIG. 1. Effect of isoprenaline ($0.25 \mu\text{g/kg}$ per min, intravenously) on (from the top) e.c.g., systemic arterial pressure (mm Hg), left ventricular pressure (mm Hg) and left ventricular dp/dt (mm Hg/s) before (on the left) and after alprenolol (1 mg/kg, intravenously, on the right). Only the first 1 min period of the infusion is shown, the infusion commencing at the vertical bars. Isoprenaline decreases arterial systolic and diastolic pressures and increases dp/dt , effects which are much reduced after alprenolol. Notice the marked Traube-Hering waves during the control infusion. Time scale (uppermost record) 1 s.

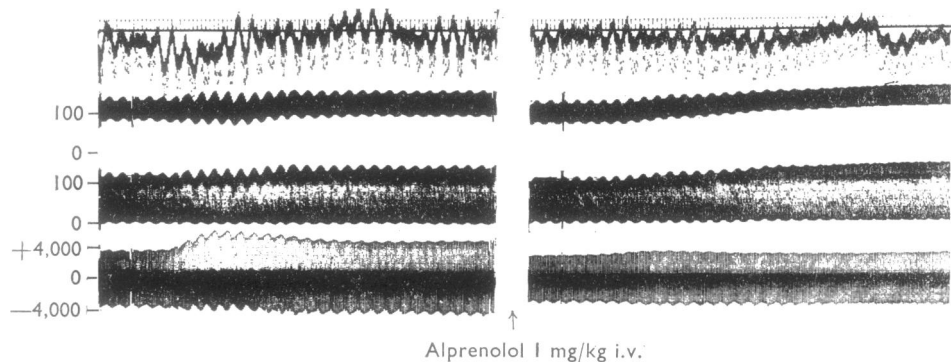


FIG. 2. Effect of adrenaline ($0.5 \mu\text{g/kg}$ per min, intravenously) on (from the top), e.c.g., systemic arterial pressure (mm Hg), left ventricular pressure (mm Hg) and left ventricular dp/dt (mm Hg/s) before (on the left) and after alprenolol (1 mg/kg, intravenously, on the right). Only the first minute period of the infusion is shown, the infusion commencing at the vertical bars. Note that the increase in dp/dt is blocked by alprenolol although the rise in peak systolic ventricular pressure is augmented. Notice the evidence of Traube-Hering waves in the early part of the control infusion period. Time scale (uppermost record) 1 s.

to an hour after, an intravenous injection of alprenolol (1.0 mg/kg). Isoprenaline infusions increased heart rate and dp/dt max and decreased systemic arterial blood pressure; these effects were all considerably reduced after alprenolol. Adrenaline infusions produced an increase in dp/dt and a small rise in heart rate, which were reduced, and a rise in diastolic arterial pressure which was augmented, after alprenolol. Infusions of noradrenaline increased dp/dt and this was reduced after alprenolol; noradrenaline-induced increases in diastolic arterial pressure and decreases in heart rate were unaffected. The control values for each measured parameter before and after alprenolol are shown in Table 1 and the catecholamine-induced changes summarized in Fig. 3. All three catecholamines slightly increased LVEDP and this was unaffected by alprenolol. LVSP was also increased by all three catecholamines; the effects of isoprenaline were reduced after alprenolol (Fig. 1) but those of adrenaline (Fig. 2) and noradrenaline were unaffected. The increase in arterial systolic pressure produced by adrenaline was very slightly (though not significantly) augmented by β -blockade. Depending on the associated change in arterial diastolic pressure, isoprenaline sometimes produced a rise and sometimes a fall in systolic pressure, so that the mean effect was negligible. In Fig. 3, those experiments in which control isoprenaline infusions produced a fall in arterial systolic pressure (that is, those in which there was also a marked fall in diastolic pressure) have been plotted separately from those in which there was a rise (associated with only a minimal change in diastolic pressure). After blockade of the effect of isoprenaline on diastolic pressure, isoprenaline produced a rise in arterial systolic pressure in both groups of experiments.

The recovery of isoprenaline responses from block by alprenolol is shown in Fig. 4. Although the degrees of block produced by doses of 0.5 and 1.0 mg/kg of alprenolol were similar, the higher dose blocked for a longer time. Inhibition of the effect of isoprenaline on arterial diastolic pressure lasted for about 2 h, while effects on heart rate and dp/dt were inhibited for only about 1 h after injection of the blocking dose. In terms of duration of action, therefore, alprenolol seems to be slightly selective for β_2 -adrenoceptors.

Infusions of all three amines increased calculated cardiac output (Table 2) and this was especially marked with isoprenaline. These effects were abolished or markedly reduced by alprenolol, which by itself had only minimal effects on cardiac output (mean change $-7 \pm 5\%$; range $+64$ to -42% ; thirty-one experiments). Changes in the "cardiac effort index" (the rate-pressure product) have been shown by Robinson (1966) to be related to the onset of pain in angina pectoris. In these experiments isoprenaline, adrenaline and noradrenaline all increased the cardiac effort index (Table 2), but only the effects of isoprenaline and adrenaline were

TABLE 1. Cardiovascular effects of alprenolol before catecholamine administration (mean \pm S.E. of mean)

	Heart rate (beats/min)	Femoral arterial pressure (mm Hg)		Left ventricular pressure (mm Hg)		Left ventricular dp/dt (mm Hg/s)	
		Systolic	Diastolic	Systolic	Diastolic	+ve	-ve
Control	201 \pm 6	132 \pm 2	79 \pm 1	119 \pm 6	6.1 \pm 0.5	4,260 \pm 180	3,390 \pm 220
Alprenolol (0.5 mg/kg)	173 \pm 7	121 \pm 1	68 \pm 6	107 \pm 4	6.1 \pm 0.6	3,360 \pm 70	3,140 \pm 270
Alprenolol (1.0 mg/kg)	178 \pm 1	126 \pm 4	66 \pm 2	117 \pm 5	7.7 \pm 0.9	3,860 \pm 120	3,330 \pm 220

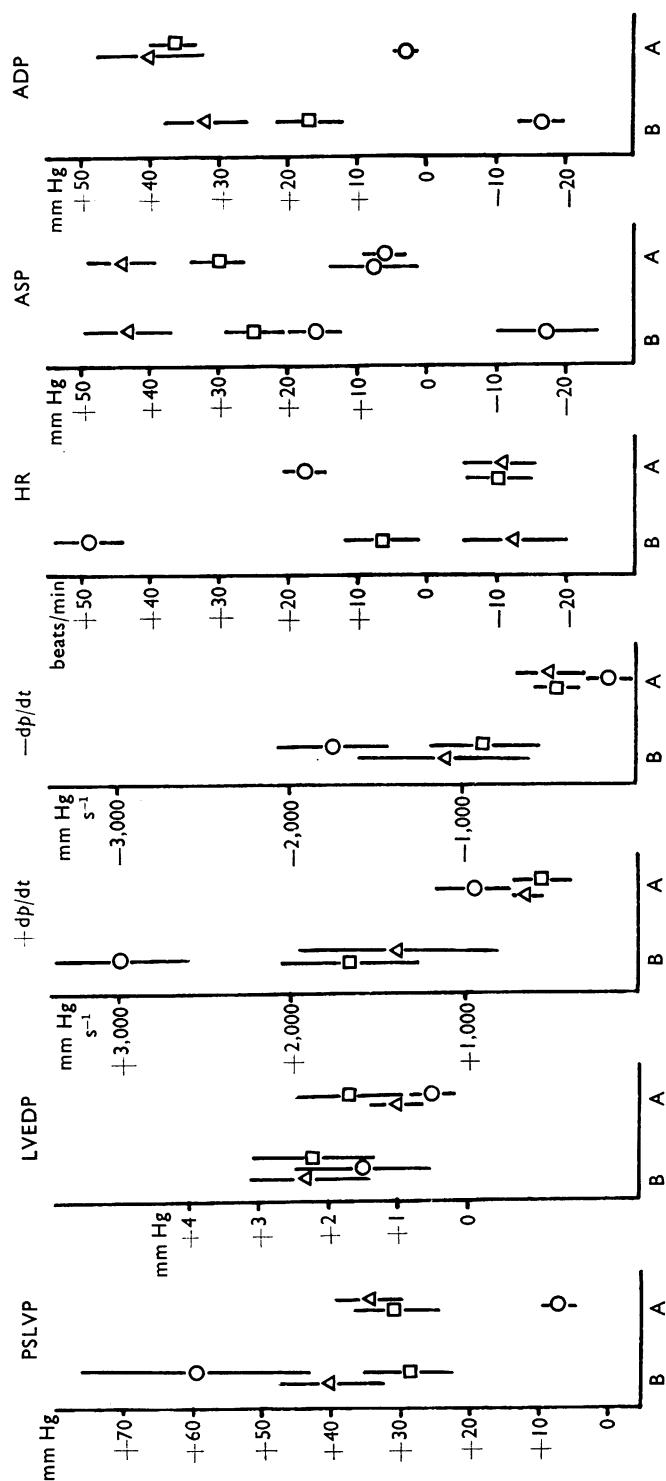


FIG. 3. Effect of isoprenaline (O), adrenaline (□) and noradrenaline (Δ) on (from the left) peak systolic left ventricular pressure (PSLVP), left ventricular end-diastolic pressure (LVEDP), +ve dp/dt, heart rate (HR), arterial systolic pressure (ASP) and arterial diastolic pressure (ADP). Changes in each parameter produced by each amine are shown before (B) and after (A) alprenolol (1 mg/kg). Each point is the mean of 5 to 17 results; the vertical lines representing the standard errors in each case. Control infusions of isoprenaline sometimes increased systolic arterial pressure and sometimes decreased it (depending on the effect on diastolic pressure). These are plotted separately (see text).

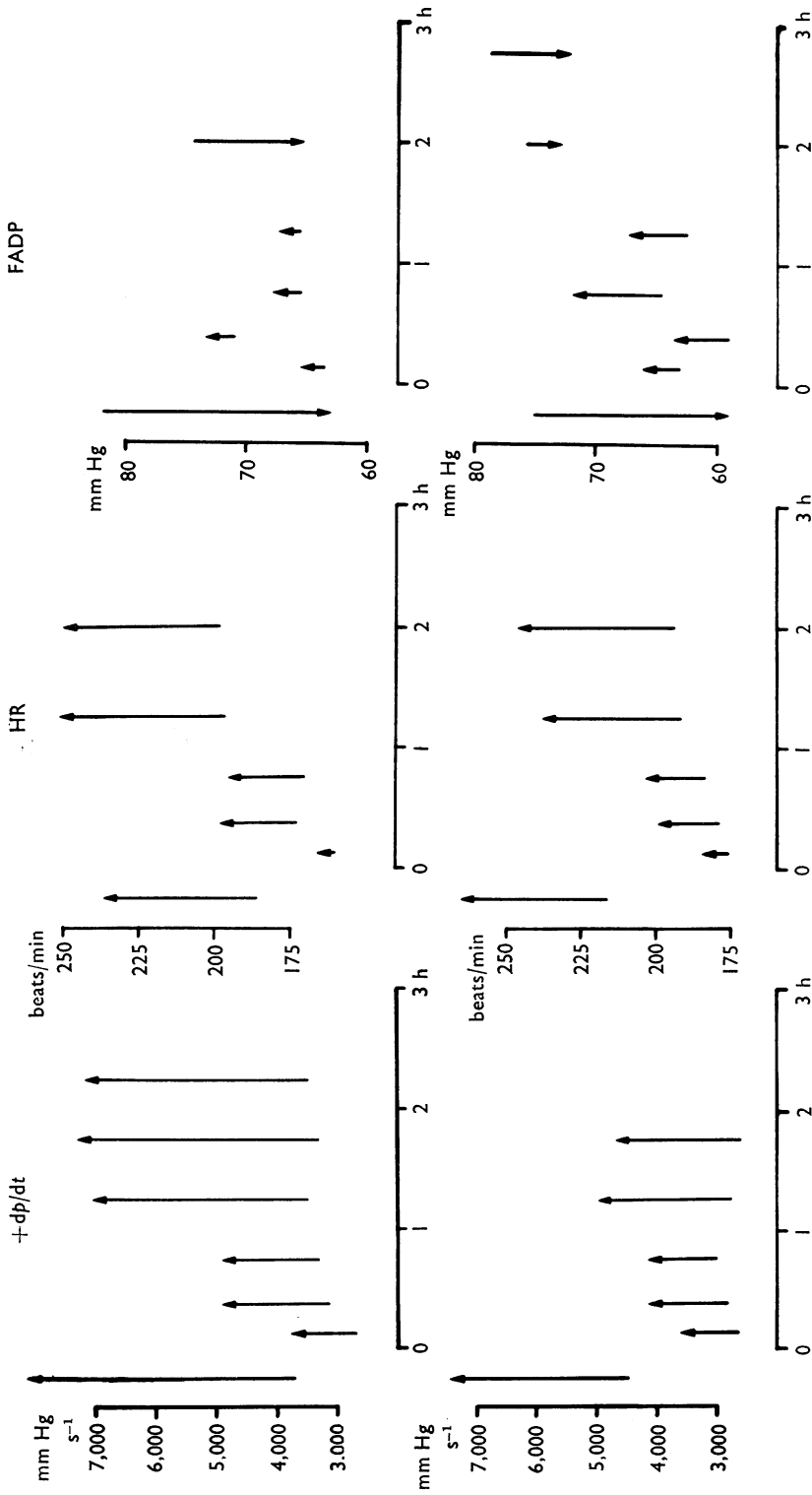


FIG. 4. Recovery of isoprenaline effects on $+ve dp/dt$ max, heart rate (HR) and femoral arterial diastolic pressure (FADP) from block by alprenolol, 0.5 mg/kg (top three graphs) and 1.0 mg/kg (lower three). The control effects are shown at the extreme left of each graph. Alprenolol was injected at zero time and the isoprenaline infusions repeated over the next 2-3 h. Each point is the mean of five to ten experiments.

reduced by alprenolol. Alprenolol alone lowered the index by $17 \pm 5\%$ (range $+37$ to -50% ; thirty-one experiments).

In occasional preparations (and particularly where the arterial pO_2 was below that necessary for 80% oxygen saturation) there was some electrocardiographic evidence of myocardial ischaemia (for example, raised ST segment). In these preparations isoprenaline sometimes intensified the ST elevation and this isoprenaline-induced myocardial ischaemic pattern was reduced after alprenolol administration.

Responses to acetylcholine

When acetylcholine is infused intravenously, bradycardia and decreases in arterial systolic and diastolic pressures and in left ventricular systolic pressure and

TABLE 2. *Effect of infusions of isoprenaline, adrenaline and noradrenaline on calculated cardiac output and on the rate-pressure product, before and after alprenolol (1.0 mg/kg) (mean % change \pm S.E.; range in brackets)*

	No. of observations	Calculated cardiac output		Rate-pressure product	
		Before alprenolol	After alprenolol	Before alprenolol	After alprenolol
Isoprenaline	13	$+68 \pm 11$ ($+18 \rightarrow +157$)	$+11 \pm 6$ ($-13 \rightarrow +36$)	$+31 \pm 7$ ($-11 \rightarrow +86$)	$+14 \pm 3$ ($+1 \rightarrow +29$)
Adrenaline	13	$+18 \pm 8$ ($-23 \rightarrow +75$)	-7 ± 4 ($-37 \rightarrow +46$)	$+21 \pm 5$ ($-4 \rightarrow +54$)	$+14 \pm 5$ ($-31 \rightarrow +39$)
Noradrenaline	6	$+27 \pm 11$ ($-4 \rightarrow +60$)	$+3 \pm 11$ ($-31 \rightarrow +47$)	$+27 \pm 9$ ($-8 \rightarrow +49$)	$+29 \pm 6$ ($0 \rightarrow +46$)

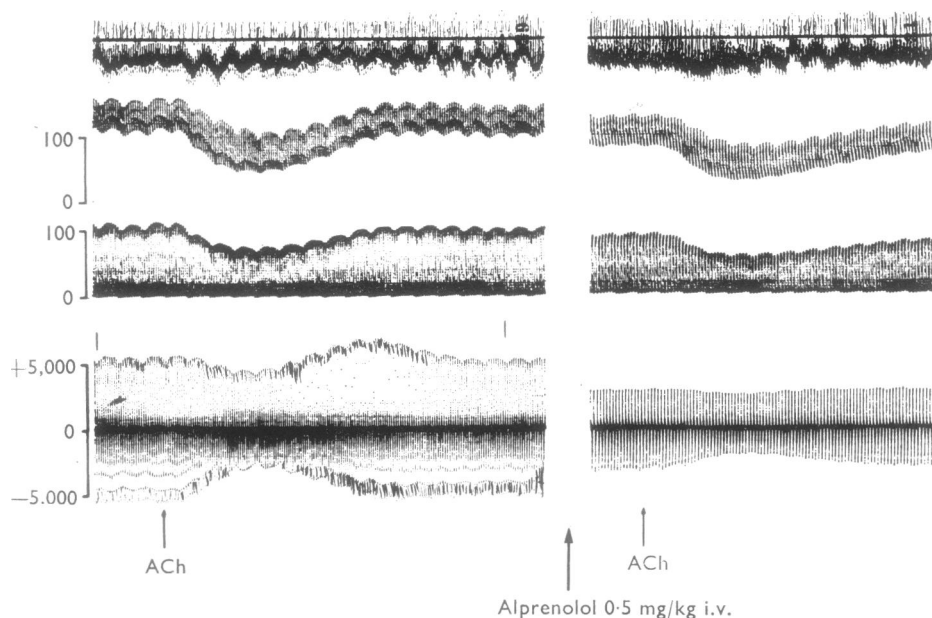


FIG. 5. Effect of injections of acetylcholine (ACh, $0.5 \mu\text{g/kg}$, intravenously at the arrows) on (from above), e.c.g., systemic arterial pressure (mm Hg), left ventricular pressure (mm Hg) and left ventricular dp/dt (mm Hg/s) before (on the left) and after alprenolol (0.5 mg/kg). Acetylcholine decreases arterial and left ventricular pressures and dp/dt but this is followed by a marked increase in dp/dt during the recovery phase. This increase is abolished after alprenolol and the recovery of both arterial and ventricular pressures is much prolonged. Time signal (uppermost trace) 1 s.

dp/dt are produced (Fig. 5). These changes are followed by an increase in dp/dt which is presumably due to a reflex stimulation of the cardiac sympathetic nerves resulting from hypotension. When the experiments were repeated after alprenolol (0.5 mg/kg) there was no reflex increase in dp/dt and the effects on systemic pressure and on left ventricular systolic pressure were considerably prolonged (see Fig. 5).

Myocardial blood flow, vascular resistance and metabolic heat production

The resting myocardial thermal conductivity increment (Δk), which is an index of local blood flow around the recorder, was 0.000514 ± 0.00006 calories/cm s °C [that is, $(5.14 \pm 0.6) \times 10^{-4}$ calories/cm s °C $\equiv (5.14 \pm 0.6) \times 10^{-4}$ c.g.s. units*, mean

* $(5.14 \pm 0.6) \times 10^{-4} \times 418.68 \text{ J m}^2 \text{ s}^{-1} \text{ °C}^{-1}$

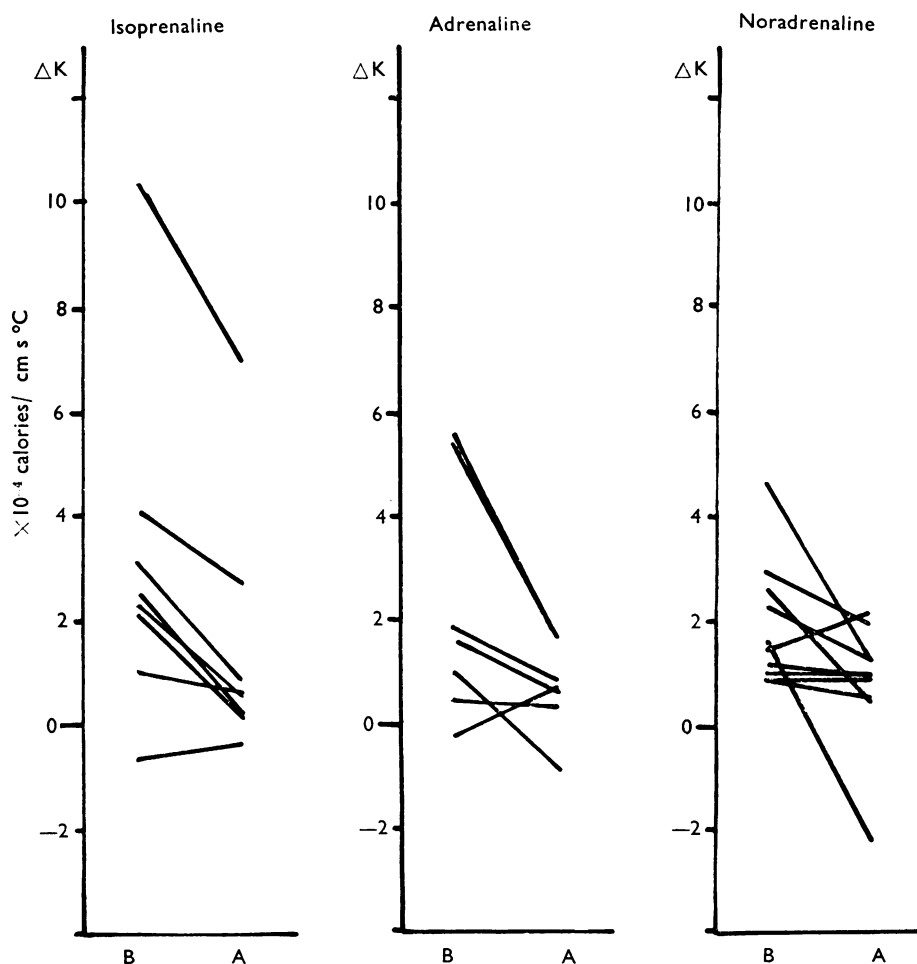


FIG. 6. Changes in myocardial blood flow (as thermal conductivity increment, Δk) produced by, from left to right, infusions of isoprenaline, adrenaline and noradrenaline before (B) and after (A) alprenolol (1.0 mg/kg). The changes produced by control infusions are given at the left of each block (B), and the effect of similar infusions after alprenolol are shown on the right (A). In almost every experiment the effects of the three amines on myocardial blood flow are much reduced by alprenolol.

of twenty-two experiments \pm S.E. of mean]. This value is very similar to that found in previous studies (McInnes & Parratt, 1969; Parratt & Wadsworth, 1969). Infusions of all three amines invariably increased myocardial blood flow, isoprenaline being the most active of the three. Thus, isoprenaline 0.25 μ g/kg per min increased myocardial blood flow by a mean of 59%, compared with mean increases of 39 and 33% with adrenaline and noradrenaline respectively (0.5 μ g/kg per min). Alprenolol (0.5 and 1.0 mg/kg) reduced but did not abolish the flow increases produced by catecholamine infusions (Fig. 6). Thus the mean increase in myocardial blood flow produced by isoprenaline after 0.5 mg/kg alprenolol was 34%, and after 1.0 mg/kg was 33%, compared with 59% before alprenolol. Adrenaline and noradrenaline increased myocardial blood flow by 16% and 11% respectively after alprenolol 1 mg/kg. The residual flow increases produced after alprenolol, expressed as a percentage of the corresponding flow increases produced before blockade, are shown in Table 3.

When the effects of changing diastolic perfusion pressure were taken into consideration, the effects of alprenolol on the myocardial vascular responses to catecholamine administration were much more striking. Adrenaline decreased myocardial vascular resistance in six out of seven experiments (mean decrease -19%) and isoprenaline in all thirteen experiments in which resistance was calculated (mean decrease -53%). After alprenolol, adrenaline increased myocardial vascular resistance and the decrease in resistance induced by isoprenaline was reduced (Fig. 7); in two experiments isoprenaline slightly increased resistance after alprenolol. Noradrenaline had rather more variable effects on resistance (mean of +22%) but again, after alprenolol, an exaggeration of this myocardial vasoconstriction was noted (Fig. 7).

An elevation of myocardial "corrected temperature" (an index of metabolic heat production) was usually observed during control catecholamine infusions. Thus increases were observed in twelve out of fifteen experiments with isoprenaline (mean increase +0.06° C), in seven out of eleven experiments with adrenaline (mean increase +0.06° C) and in five out of six experiments with noradrenaline (mean increase +0.04° C). When decreases in "corrected temperature" occurred they were usually very small (< -0.03° C). With isoprenaline, the effect on calculated heat production was markedly reduced after alprenolol (1.0 mg/kg) in all except one experiment (mean decrease -0.03° C; a net change of -0.09° C). The results from a typical experiment are illustrated in Fig. 8. Alprenolol also reduced the calorigenic effect of adrenaline and noradrenaline (net change in each case -0.04° C).

There was no correlation between catecholamine-induced changes in calculated heat production ("corrected temperature") and changes in heart rate, left

TABLE 3. *Effect of catecholamines on myocardial blood flow*

	Dose of alprenolol (mg/kg i.v.)	Flow increase after alprenolol Flow increase before alprenolol $\times 100$	Significance of residual catechol- amine effect
Isoprenaline	1.0	39 \pm 10*	0.1 -0.005
Isoprenaline	0.5	39 \pm 12†	0.025-0.02
Adrenaline	1.0	34 \pm 10†	0.05 -0.025
Noradrenaline	1.0	30 \pm 12	

Significance of alprenolol effect: * $P < 0.001$; † $P < 0.005$.

The increase in flow produced by catecholamine infusions after alprenolol is expressed as a percentage of the increase in flow produced by corresponding infusions before alprenolol.

ventricular dp/dt , cardiac output or calculated oxygen consumption, which was derived both from the product of heart rate and mean arterial pressure (the "cardiac effort index" of Feinberg *et al.*, 1962) and of heart rate and systolic arterial (or peak left ventricular) pressure—the rate-pressure product described by Robinson (1966).

Liver blood flow, vascular resistance and heat production

The mean control liver thermal conductivity increment was 3.7×10^{-4} calories/cm s °C, and this was elevated during the infusion of isoprenaline (mean increase \pm S.E.,

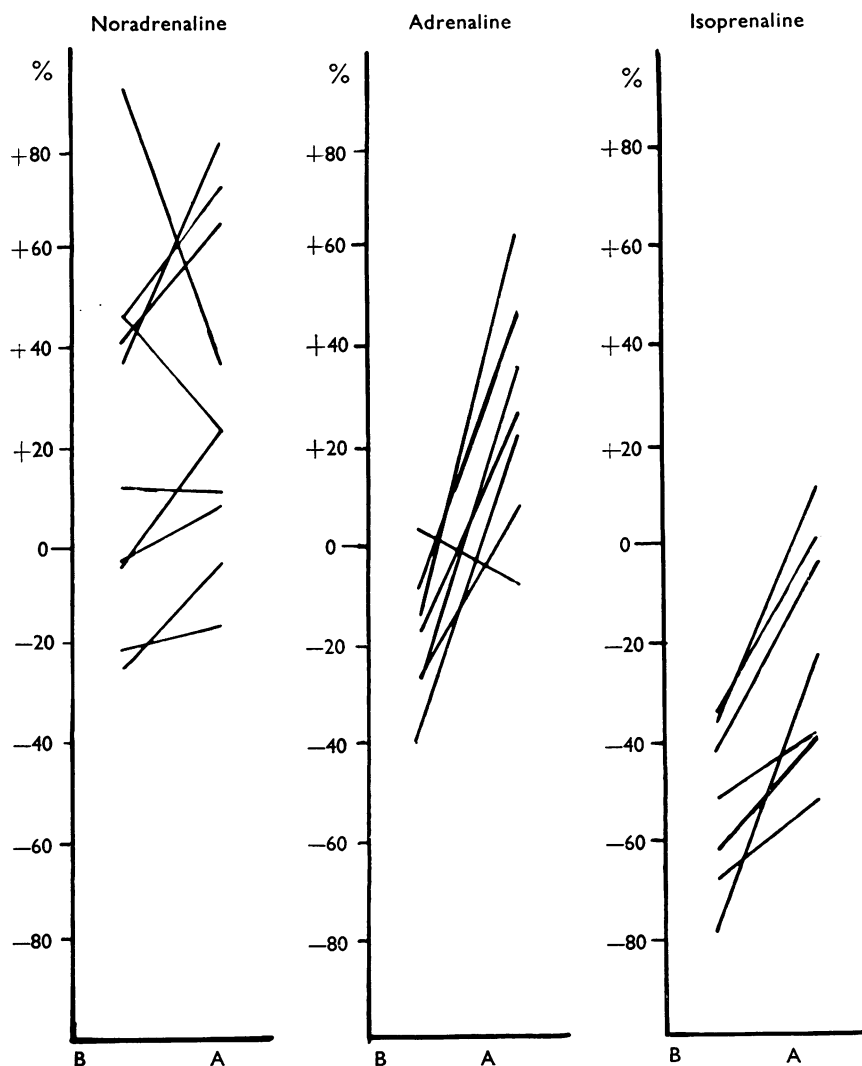


FIG. 7. Changes in calculated myocardial vascular resistance (systemic arterial pressure, mm Hg/myocardial thermal conductivity increment; Δk , $\times 10^{-4}$ calories/cm s °C), expressed as % of pre-infusion values, produced by (from the left) noradrenaline, adrenaline ($0.5 \mu\text{g/kg}$ per min) and isoprenaline ($0.25 \mu\text{g/kg}$ per min) before (on the left of the blocks) and after alprenolol (1.0 mg/kg). In most instances decreases in resistance caused by the amines were reduced or reversed following alprenolol administration.

0.92 ± 0.46), adrenaline (by 1.52 ± 0.55) and of noradrenaline (by 0.88 ± 0.12). These increases in blood flow induced by isoprenaline and by noradrenaline (25 and 24% respectively) were much less than those observed in the myocardium (59 and 33% respectively) after similar doses, whereas adrenaline increased liver blood flow and myocardial blood flow to about the same extent (41 and 39% respectively). These increases in liver blood flow were almost abolished following β -adrenoceptor blockade with alprenolol (1.0 mg/kg), the mean changes being 0.32 ± 0.16 , 0.31 ± 0.14 and $0.14 \pm 0.28 \times 10^4$ calories/cm s $^{\circ}\text{C}$ (9, 8 and 4%) for isoprenaline, adrenaline and noradrenaline respectively.

The effects of the three amines on liver vascular resistance (calculated from integrated mean arterial pressure, mm Hg/liver thermal conductivity increment $\times 10^{-4}$ calories/cm s $^{\circ}\text{C}$) are illustrated in Fig. 9. Isoprenaline decreased liver vascular resistance and, except in one experiment, this was reduced or reversed after alprenolol; adrenaline decreased vascular resistance and this was reversed after alprenolol, while noradrenaline usually increased resistance and this was potentiated after alprenolol.

Small increases in liver metabolic heat production occurred during the infusion of each of the amines (means of $+0.017$, $+0.05$ and $+0.065^{\circ}\text{C}$ respectively with isoprenaline, adrenaline and noradrenaline). After alprenolol these effects were slightly (but not significantly) reduced (0.013 , 0.02 and 0.05°C).

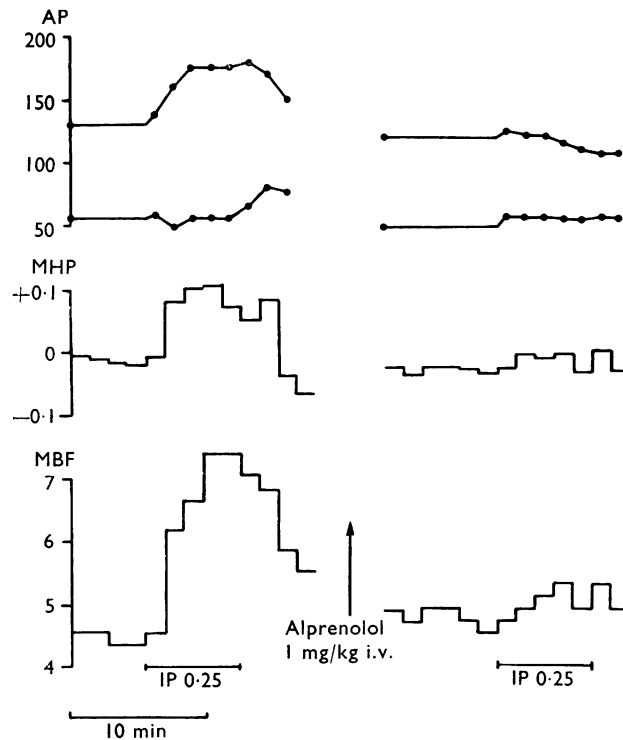


FIG. 8. Effect of isoprenaline (IP, $0.25 \mu\text{g/kg}$ per min, intravenously, during the horizontal bars) on (from above) arterial pressure (AP) (mm Hg), myocardial metabolic heat production (MHP) (as "corrected temperature", $^{\circ}\text{C}$) and on myocardial blood flow (MBF) (as thermal conductivity increment, $\Delta k, \times 10^{-4}$ calories/cm s $^{\circ}\text{C}$) before (on the left) and after (on the right) alprenolol (1.0 mg/kg).

Extravascular smooth muscle

In order to differentiate more clearly between effects on β_1 - and β_2 -adrenoceptors, air-way resistance and spontaneous pendular movement of the small intestine were recorded in some of the experiments. Isoprenaline generally caused a reduction in air-way resistance which was blocked by alprenolol, while noradrenaline and adrenaline usually increased air-way resistance and this was usually intensified after alprenolol (see Fig. 10). It is clear from Figs. 1 and 2 that the doses of adrenaline and isoprenaline used sometimes stimulated respiration and on occasions the animals attempted to breathe against the pump. This may have contributed towards the increase in air-way resistance observed, for example with adrenaline, because in isolated bronchial and tracheal smooth muscle preparations it is well established that this amine causes relaxation. That a β component is present, however, is clear from the fact that adrenaline- and noradrenaline-induced increases in air-way resistance were intensified after alprenolol (see Fig. 10).

Adrenaline and noradrenaline always inhibited intestinal smooth muscle movement and this was unaffected by alprenolol (Fig. 11). On some occasions iso-

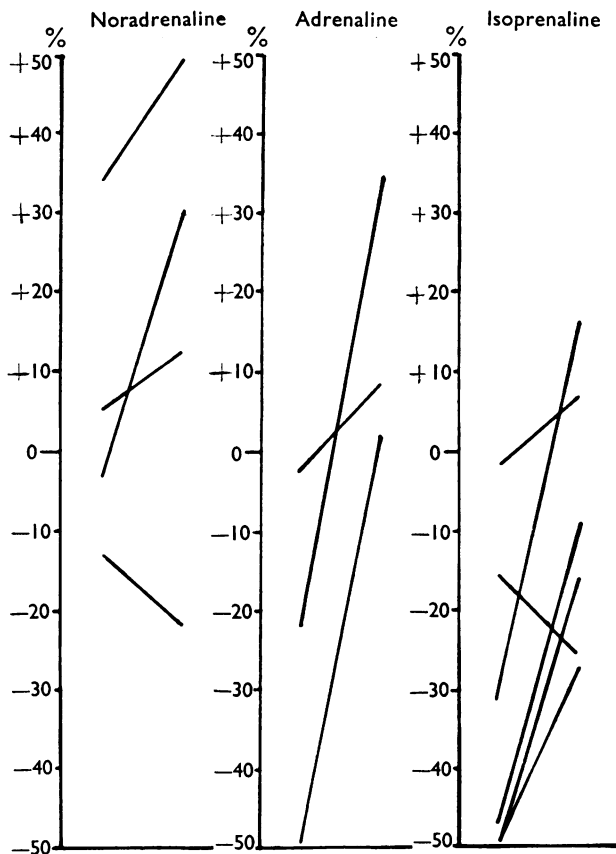


FIG. 9. Effect of (from the left) noradrenaline, adrenaline ($0.5 \mu\text{g/kg}$ per min) and isoprenaline ($0.25 \mu\text{g/kg}$ per min) on calculated liver vascular resistance (mean arterial blood pressure mm Hg/liver thermal conductivity increment Δk) expressed as a % of pre-infusion values before (on the left of the blocks) and after (on the right) alprenolol (1.0 mg/kg).

prenaline inhibition of gut pendular movement was preceded by stimulation. The inhibitory phase was blocked by alprenolol (Fig. 11).

Discussion

In these experiments we have attempted to measure the effect of catecholamines on myocardial blood flow, myocardial heat production and on a number of haemodynamic variables, before and after β -adrenoceptor blockade with alprenolol. In order to assess adequately the relevance of blood flow changes we felt it important to measure changes both in cardiac contractility and in output; in small animals such as the cat this presents a number of problems if one is to keep operative surgery to a minimum. We have assessed cardiac contractility from the

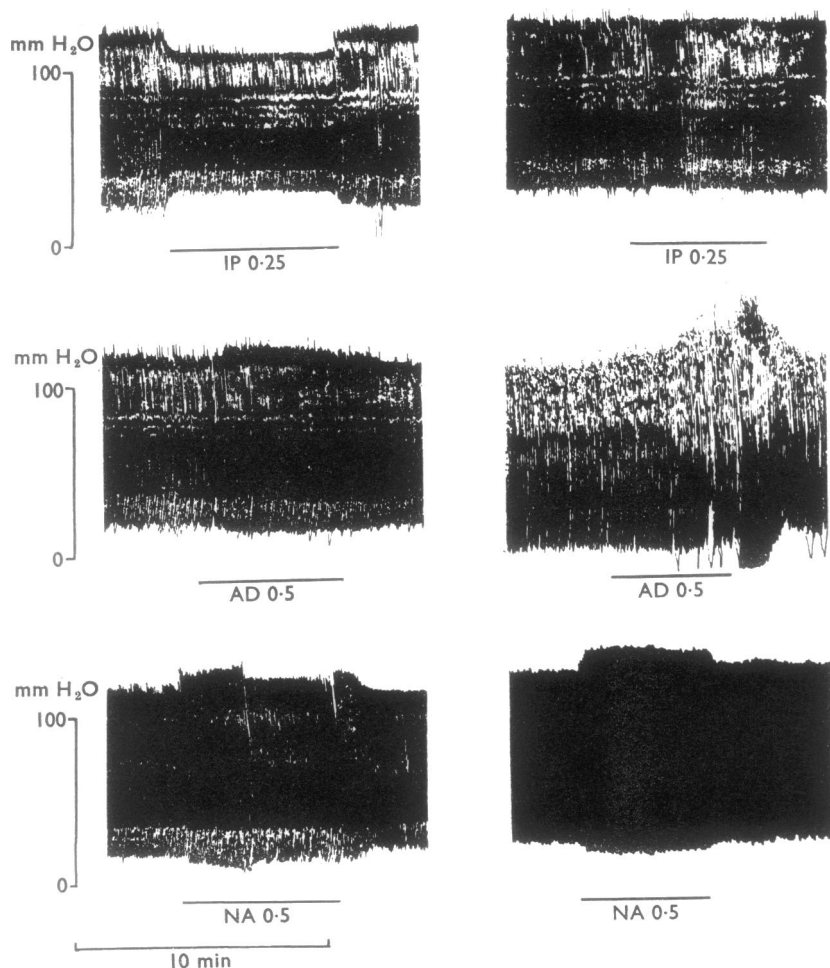


FIG. 10. Effect of infusions (at the horizontal bars) of, from above, isoprenaline (IP, 0.25 $\mu\text{g/kg per min}$), adrenaline (AD) and noradrenaline (NA) (0.5 $\mu\text{g/kg per min}$) on air-way resistance (mm H₂O) before (on the left) and after alprenolol (1.0 mg/kg on the right). Isoprenaline reduced air-way resistance and this was prevented by alprenolol; adrenaline and noradrenaline tended to increase air-way resistance and this was exaggerated by alprenolol. Time bar 10 min.

rate of rise of the left ventricular pressure pulse (dp/dt), as suggested by Hamacher (1960, 1963) and by Benfey, Greeff & Heeg (1967). The validity of this method has been reviewed by Gleason & Braunwald (1962), Wallace, Skinner & Mitchell (1963) and by Schaper, Lewi & Jageneau (1965). Provided LVEDP is adequately monitored, dp/dt max is a useful index of cardiac contractility which can be used in closed-chest, spontaneously breathing, preparations. The assessment of cardiac output is more difficult. Of the three methods most frequently used in larger animals, the thermodilution technique is not possible in our preparations because the injection of cold saline interferes with the measurement of metabolic heat production. The direct Fick and the dye-dilution methods are unsuitable in rapidly changing situations such as occur during catecholamine administration. The assess-

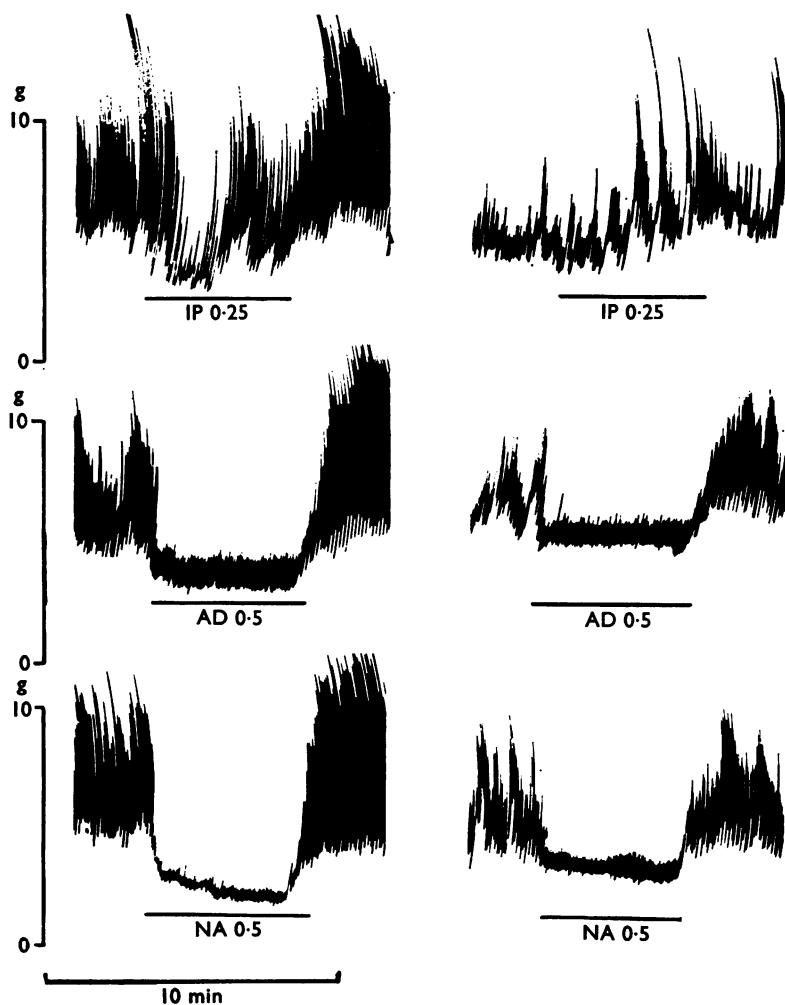


FIG. 11. Effect of intravenous infusions (at the horizontal bar) of, from above, isoprenaline (IP, 0.25 $\mu\text{g/kg per min}$), adrenaline (AD) and noradrenaline (NA) (0.5 $\mu\text{g/kg per min}$) on *in vivo* intestinal movement (measured with a strain gauge) before (on the left) and after alprenolol (1.0 mg/kg on the right). All three amines inhibit intestinal movement (particularly adrenaline and noradrenaline) but only the effect of isoprenaline is modified by alprenolol.

ment of the stroke volume from the aortic pressure pulse is based on the fact that the amount of rise of pressure in the arterial system depends on (a) the stroke volume and (b) the arterial distensibility (see Burton, 1965). If we ignore the escape of blood from the artery during the anacrotic limb then stroke volume = pulse pressure \times arterial distensibility and this is the basis of the early "pulse contour" method of estimating cardiac output. Within the same animal this gives a reasonable index of cardiac output. A variant of this method is to measure the rate of rise of pressure within the aorta (aortic dp/dt) rather than the actual pressure rise itself (Jones, Hefner, Bancroft & Klip, 1959; Greenfield *et al.*, 1962). In dogs, both methods correlate well with the direct measurement of aortic flow with an electromagnetic flowmeter (Greenfield *et al.*, 1962) and with dye-dilution (Ledingham & Parratt, unpublished observations) and give, at very least, semi-quantitative indications of changes in cardiac output induced by drugs.

Before alprenolol, all three amines increased pulse pressure, calculated cardiac output, left ventricular peak systolic pressure and left ventricular dp/dt max. These effects, which were particularly pronounced with isoprenaline, were markedly reduced after alprenolol. This implies that the release of adrenaline and noradrenaline, which occurs in angina, will have less effect on myocardial work and oxygen consumption in the presence of alprenolol. One way to assess this is by the use of the rate-pressure product. Robinson (1966) has shown that this is closely related to the onset of pain in anginal patients. Our experiments show that this is reduced after alprenolol only for adrenaline and isoprenaline but not for noradrenaline. However, alprenolol itself causes a reduction in the rate-pressure

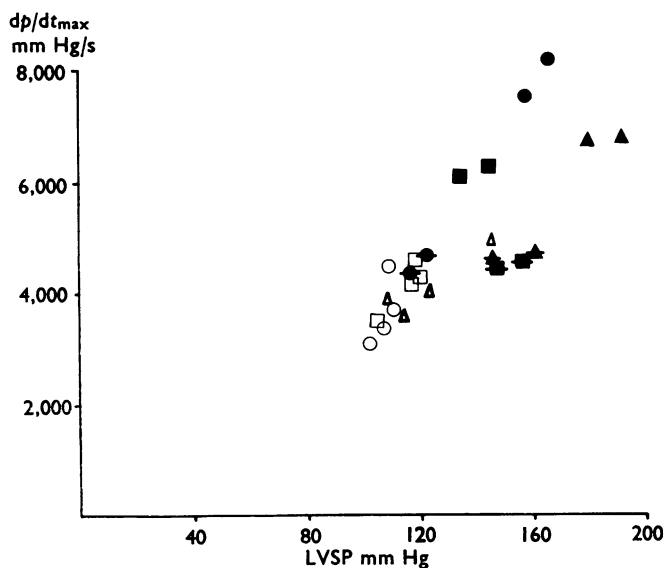


FIG. 12. Relationship between peak left ventricular systolic pressure (LVSP, mm Hg) and left ventricular dp/dt max (mm Hg/s) at rest (open symbols) and after infusions of isoprenaline (●), adrenaline (■) and noradrenaline (▲); corresponding effects after alprenolol are shown as -●-, -■- and -▲- respectively. There is a good correlation with isoprenaline (both before and after β -adrenoceptor blockade) and with adrenaline (before blockade) but there was a marked shift to the right with noradrenaline and with adrenaline after β -adrenoceptor blockade. Details in Discussion.

product of about 17% and the product calculated during the infusion of noradrenaline in alprenolol treated cats was only 9% greater than in the control (pre-alprenolol and pre-noradrenaline) situation. One might reasonably conclude, therefore, that in the patient with angina, alprenolol would increase the time taken for the onset of pain during cardiac effort. Certainly, in the present experiments it reduced the ischaemic electrocardiographic pattern induced by catecholamines in the relatively hypoxic myocardium.

One recognized omission in this study is that there has been no direct measurement of myocardial oxygen consumption. However, this is related closely to the "cardiac effort index" (mean aortic pressure \times heart rate; Feinberg *et al.*, 1962), to the tension-time index (the area under the aortic pressure curve; Sarnoff, Braunwald, Welch, Case, Stainsby & Macruz, 1958) and to the rate of rise of pressure development within the left ventricle (Sonnenblick, Ross & Braunwald, 1968). If we use cardiac effort indices as indications of myocardial oxygen consumption, it is clear from our studies that (a) it is increased by catecholamines and (b) that this effect is slightly reduced by alprenolol. These conclusions are probably valid, although it is certain that all these indices of oxygen consumption are oversimplified and that the two main factors determining the consumption of oxygen by the myocardium are the development of intramyocardial tension and the contractile state (that is, the velocity of contraction; Sonnenblick *et al.*, 1968).

In a recent paper Greeff, Mellinghoff & Schlieper (1969) have suggested that drugs which possess a positive inotropic action can be divided into two main groups. In isolated perfused guinea-pig hearts they showed that digitoxigenin and calcium chloride increased peak left ventricular systolic pressure and left ventricular dp/dt max to the same extent, whereas histamine and noradrenaline preferentially raised dp/dt max. It was of interest to see whether this conclusion applied also to the heart *in vivo*. In fact, and as Gleason & Braunwald (1962) have demonstrated in man, there was a fairly good correlation between peak ventricular systolic pressure and dp/dt in the control animals and in those given isoprenaline, both before and after alprenolol (Fig. 12). With noradrenaline, and with adrenaline after alprenolol, there was a marked shift in the curve to the right; in other words, peak systolic pressure was increased more than the rate of development of this pressure. It is possible that this is partly due to the increased aortic resistance, although increased after-load in normal animals is associated not only with increased peak ventricular pressure but also with increased pressure development (Wiggers, 1928). However, it clearly enables us to differentiate between the actual pressure developed within the ventricle and the rate of rise of this pressure. It is only the effect of adrenaline and noradrenaline on the latter, which is an index of contractility, that is antagonized by β -adrenoceptor blocking drugs.

The effect of alprenolol on the response of the myocardial circulation to catecholamines was similar to that already described for propranolol and other β -adrenoceptor blocking drugs. Adrenaline and noradrenaline increased myocardial vascular resistance after alprenolol, as they do after pronethalol (Parratt, 1965) and propranolol (Gaal, Kattus, Kolin & Ross, 1966) and this suggests that α -adrenoceptors are present in the myocardial vascular bed of the cat as well as in that of the dog and monkey (see Parratt, 1967, 1969). All three amines usually increased myocardial metabolic heat production and this effect was also reduced by alprenolol, a finding similar to that described for propranolol (Parratt, 1969). Although

"corrected temperature" can only remain a qualitative measurement, there was no correlation between this index of heat production and pressure development, cardiac output or heart rate. Other factors are clearly involved. Thus Gibbs has drawn attention to the fact that in cardiac muscle there are two main components of heat production. One is tension (and muscle length) independent (and is perhaps equivalent to activation heat in skeletal muscle), the other is the additional heat liberated when a muscle shortens or develops tension (Gibbs, 1967a, b; Gibbs, Mommaerts & Ricchiuti, 1967). It is not therefore surprising that we have failed to demonstrate a correlation with tension development alone. It seems likely that our measurements of heat production are indicative, not only of the increased cost of energy development (additional heat) but also of resting heat, which can occur in the absence of muscle contraction. It is the latter which is probably related to the "calorigenic" effect of catecholamines; that is, the increase in oxygen consumption which cannot be explained solely by changes in internal and external cardiac work.

Unpublished experiments in dogs (Ek & Åblad, personal communication) have demonstrated that alprenolol in a dose of 0.3 mg/kg practically abolishes the effects of cardiac sympathetic nerve stimulation. In our experiments larger doses (0.5 and 1.0 mg/kg) failed to antagonize completely the effects of infused catecholamines on dp/dt and on myocardial blood flow, although the smaller dose of alprenolol completely abolished the reflex increase in dp/dt which occurred during the recovery phase from acetylcholine administration. It is unusual for receptor blocking drugs to antagonize preferentially the effects of transmitters released from nerve endings rather than those of exogenous agonists, and it is possible that alprenolol possesses some adrenergic neurone blocking activity as well as β -receptor blocking activity. Preliminary evidence from isolated smooth muscle preparations (Wadsworth, unpublished) suggests that this is in fact so.

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