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Myocardial and haemodynamic effects of the beta-adrenoceptor blocking drug alprenolol (H56/28) in anaesthetized cats

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1. The effects of the beta-adrenoceptor blocking drug alprenolol (H56/28) on myocardial and general haemodynamics were studied in anaesthetized cats.

2. Alprenolol (0·5 mg/kg and 1·0 mg/kg) reduced femoral systolic and diastolic pressures, heart rate and left ventricular systolic pressure. The rate of rise of the left ventricular pressure pulse (dp/dt) was reduced despite a significant elevation of left ventricular end-diastolic pressure. This is evidence for decreased myocardial contractility. On some occasions there was a transient initial increase in +ve dp/dt max. possibly indicative of moderate β-adrenoceptor stimulant activity.

3. Myocardial and liver blood flows were measured using a heated thermocouple technique. Alprenolol slightly decreased both myocardial and liver blood flows (mean of 17% and 15% respectively with a dose of 1·0 mg/kg). Myocardial and liver vascular resistances were only very slightly increased.

4. Alprenolol had no direct effect on calculated myocardial and liver metabolic heat production.

5. In doses up to 1·0 mg/kg alprenolol had no effect on airway resistance but occasionally decreased (*in vivo*) intestinal muscle movement.

6. Since alprenolol (although reducing calculated myocardial oxygen consumption and the myocardial and metabolic heat stimulant effects of catecholamines) has no significant effect on myocardial vascular resistance, it is suggested that it would be a useful adjunct in the therapy of angina pectoris.

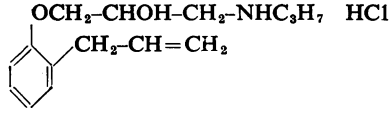
The introduction of the β-adrenoceptor blocking drugs, particularly of propranolol, into clinical medicine has resulted in a significant advance in the treatment of angina pectoris (Rabkin, Stables, Levin & Suzman, 1966 ; Epstein & Braunwald, 1968). The mechanism by which propranolol benefits the anginal patient is almost certainly by reducing myocardial oxygen demand. Decreases occur in arterial pressure, the velocity of myocardial contraction, the rate of change of the left ventricular pressure pulse and of exercising (and resting) heart rate (Robin, Cowan, Puri, Ganguly, DeBoyrie, Martinez, Stock & Bing, 1967 ; Dwyer, Wiener & Cox, 1968 ;

Lewis & Brink, 1968), all changes that reduce the oxygen needs of the myocardium. In addition, propranolol reduces the increase in metabolic heat production induced in the myocardium by adrenaline (Parratt, 1969).

It may seem paradoxical, however, that this undoubtedly beneficial anti-anginal drug reduces myocardial blood flow (Parratt & Grayson, 1966; Stein, Brooks, Matson & Hyland, 1968), increases myocardial vascular resistance to flow (Nayler, McInnes, Swann, Carson & Lowe, 1967; Whitsitt & Lucchesi, 1967; Laubie & Drouillat, 1968) and reverses coronary vasodilatation induced by catecholamines (Gaal, Kattus, Kolin & Ross, 1966; Parratt, 1969).

A proportion of the decrease in myocardial blood flow that occurs with propranolol is clearly related to decreases in myocardial oxygen demand, but it is also likely that part is the result of blockade of myocardial vascular beta-receptors (Parratt, 1967a). Recently, it has become clear that there are at least three types of beta-receptor blocking drugs. There are those drugs that are able to selectively block myocardial (β_1) but not vascular (β_2) receptors (such as I.C.I. 50172; Dunlop & Shanks, 1968); those that can selectively block vascular but not myocardial β-receptors (such as butoxamine, dimethyl isopropylmethoxamine (Levy, 1966; Wilkenfeld & Levy, 1968) and H35/25 (Levy & Wilkenfeld, 1969)) and those that block both types of receptor (such as propranolol, pronethalol and MJ 1999). Theoretically the best beta-receptor blocking drugs to use in angina would be those (like I.C.I. 50172) that decrease cardiac oxygen consumption (by blocking myocardial (β_1) adrenoreceptors) without blocking the direct vasodilator effects of released sympathetic transmitters (Parratt & Wadsworth, unpublished).

One further problem in the clinical use of beta-adrenoceptor blocking drugs in angina is the danger of reducing cardiac sympathetic drive to the extent of precipitating heart failure, especially in patients with poor initial cardiac contractility. Myocardial contractility is depressed by propranolol both at rest and during exercise (Robin *et al.*, 1967; Dwyer *et al.*, 1968) and there is evidence for a raised left ventricular end-diastolic pressure despite diminished stroke work (Lewis & Brink, 1968). Alprenolol (H56/28, Aptin, I-(*o*-allylphenoxy)-3-isopropylamino-2-propanol; Brändström, Corrodi, Junggren & Jönsson, 1966; Åblad, Brogård & Ek, 1967) is a beta-adrenoceptor blocking drug



introduced in an attempt to overcome these disadvantages, because it is claimed to possess moderate β-adrenoceptor stimulant activity (that is, it is a partial agonist of β-adrenoceptors). Thus, whereas propranolol reduces cardiac output in man (Forsberg & Johnsson, 1967; Lewis & Brink, 1968) and markedly increases peripheral vascular resistance, alprenolol has minimal effects on cardiac output (Forsberg & Johnsson, 1967). It seemed therefore of interest to examine the effects of alprenolol on the myocardial circulation with particular reference to its effect on myocardial contractility, vascular resistance and metabolic heat production. A subsequent publication (Parratt & Wadsworth, unpublished) will describe the effects of catecholamine infusions on these parameters before and after alprenolol.

Methods

Twenty-one cats of both sexes and weighing between 2·0 and 3·8 kg. were anaesthetized with sodium pentobarbitone (30 mg/kg by intraperitoneal injection). Body temperature was maintained between 36·5° and 38·0° C and was measured by direct recording thermocouples in the rectum, the aortic arch and the mid-oesophagus. The trachea was cannulated and positive pressure ventilation commenced at thoracotomy with room air. This was continued throughout the experiment in order to eliminate changes in heat loss from the surface of the heart. The respiratory stroke volume was between 40 and 65 ml. and the rate 30/min. Arterial blood pO_2, pCO_2 and pH were measured using micro-electrodes (Radiometer, Copenhagen).

Blood flow in the muscle of the left myocardium was measured in eleven cats using a modification of the heated thermocouple technique described by Grayson & Mendel (1961). Full experimental details of the method and of the calculations for assessing myocardial thermal conductivity (an index of blood flow, Grayson & Parratt, 1966) and of " corrected temperature " (an index of metabolic heat production ; Dosekun, Grayson & Mendel, 1960 ; Parratt, 1969) have been described in a recent publication (McInnes & Parratt, 1969). In five cats, liver blood flow and heat production were measured with heated thermocouples. The method was similar to that described by Grayson & Kinnear (1958) except that the output from the thermocouples was fed directly into a Kipp and Zonen micrograph BD5 ink writing recorder (100 or 200 μV for a full scale deflection of 20 cm). In these experiments (as in those in which myocardial blood flow was measured) the cold junction was positioned in the aortic arch and is thus probably not truly representative of afferent liver blood temperature.

Arterial blood pressure (descending aorta), right atrial pressure and left ventricular pressure were measured with capacitance transducers (Elema-Schönander types EMT 35, 33 and 34 respectively) and the rate of rise ($+$ve dp/dt, an index of myocardial contractility) and fall ($-$ve dp/dt) of ventricular pressure by an analog differentiator circuit previously described (McInnes & Parratt, 1969). In some of the experiments the metal catheter used to record ventricular pressure was not introduced by way of the right carotid artery (as in previous experiments) but by puncture of the left ventricular wall immediately after the insertion of the blood flow recorder. In these animals it was thus possible to measure simultaneously myocardial blood flow and dp/dt. Left ventricular pressure, left ventricular end-diastolic pressure (LVEDP), arterial pressure, right atrial pressure, dp/dt and the e.c.g. (leads II or III) were recorded on an eight-channel Elema-Schönander recorder (Mingograph 81). For the measurement of the P-R interval and the rate of rise of the arterial pressure pulse (which gives a reasonable approximation, within the same animal, of the stroke volume, Greenfield, Patel, Barnett & Fox, 1962), the paper speed was 250 mm/sec. In a few experiments the rate of rise of the descending aortic pulse with time (aortic dp/dt) was continuously determined with an analog differentiator circuit similar to that used for ventricular dp/dt.

In order to assess the effect of alprenolol on extravascular beta-adrenoceptors, duodenal or jejunal movement was measured with an isometric strain gauge (Ugo-Basile) sutured to the wall of the intestine ; the abdominal wall was closed in two layers. The output from the gauge was amplified and fed either into a moving-coil

galvanometer writing on a smoked drum or into the Mingograph 81. Assessments of bronchial smooth muscle resistance (or more accurately, airway resistance) were made by attaching a Palmer saline manometer (writing on a smoked drum) to the input arm of the tracheal cannula.

Results

General haemodynamic effects of alprenolol

Alprenolol (0·5 mg/kg) decreased systolic pressure (by a mean of 10 ± 2 mm Hg), diastolic pressure (by a mean of 10 ± 3 mm Hg), heart rate (by 23 ± 5 beats/min) and +ve dp/dt (by $1{,}130 \pm 290$ mm Hg/sec). The effects of the larger dose used

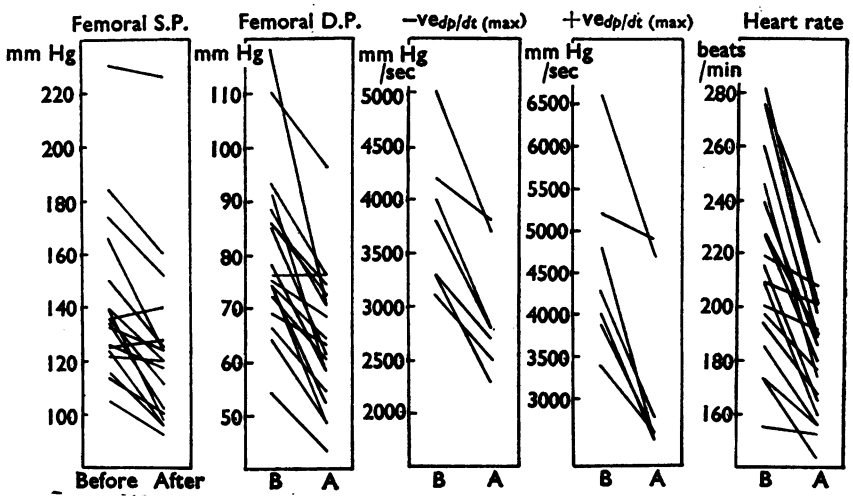


FIG. 1. Effect of alprenolol (1·0 mg/kg intravenously) on systolic and diastolic pressures (mm Hg), left ventricular dp/dt (mm Hg/sec) and heart rate (beats/min) in anaesthetized cats.

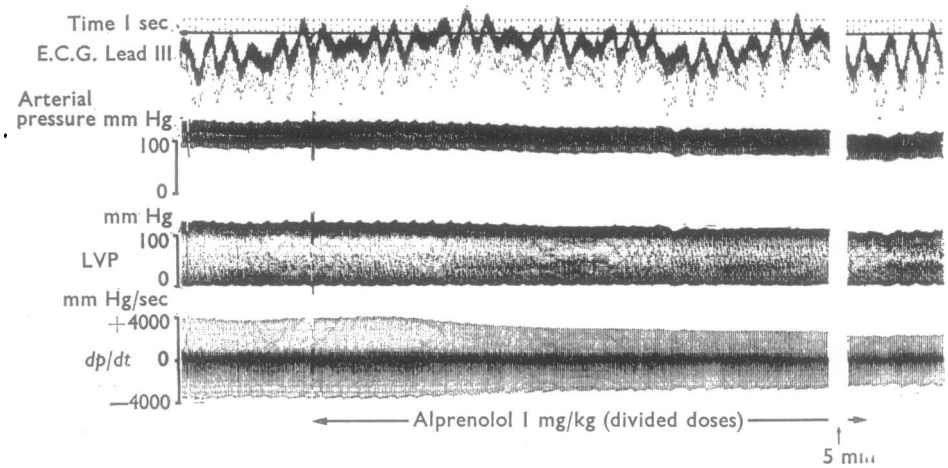


FIG. 2. Effect of an intravenous injection of alprenolol (1·0 mg/kg; at the vertical line) on (from below upwards) left ventricular dp/dt (mm Hg/sec), left ventricular pressure (mm Hg) and arterial pressure (mm Hg). There is a decrease in myocardial contractility (+ve dp/dt) preceded by a slight initial increase. Time marker 1 sec.

(1·0 mg/kg) were similar and are illustrated in Fig. 1. Systolic pressure was reduced from a mean of 141 to a mean of 126 mm Hg, diastolic pressure from 80 to 65 mm Hg, heart rate from 220 to 180 beats/min, +ve dp/dt from 4,600 to 3,230 mm Hg/sec and −ve dp/dt from 3,810 to 2,940 mm Hg/sec. The result from one experiment is illustrated in Fig. 2. Occasionally there was a slight initial increase in +ve dp/dt (as in Fig. 2), probably indicative of some β-receptor stimulant activity (Ablad *et al.*, 1967). Left ventricular systolic pressure fell from 117±3 mm Hg to 110±4 mm Hg with a dose of 0·5 mg/kg of alprenolol and from 121±6

TABLE 1. *Effect of alprenolol (0·5 mg/kg intravenously) on myocardial blood flow (as thermal conductivity increment, Δk, c.g.s. units $\times 10^{-4}$) and on myocardial vascular resistance (diastolic blood pressure mm Hg/Δk)*

Expt. No.	Myocardial thermal conductivity			Myocardial vascular resistance		
	Before Alprenolol	After Alprenolol	% Change	Before Alprenolol	After Alprenolol	% Change
18/12	9·0	7·6	−16	11·8	11·9	—
08/01	8·5	8·4	−1	5·9	6·6	+12
15/01	8·1	7·7	−5	8·2	7·3	−11
17/01	2·3	1·4	−39	34·5	47·8	+39
21/01	5·7	4·7	−18	11·2	11·2	—
08/04	3·1	3·3	+6	26·6	21·4	−20
10/64	2·9	3·3	+14	35·1	24·4	−30
11/04	2·6	1·9	−27	30·5	38·5	+26
Mean	5·3	4·8	−11	20·5	21·1	+2

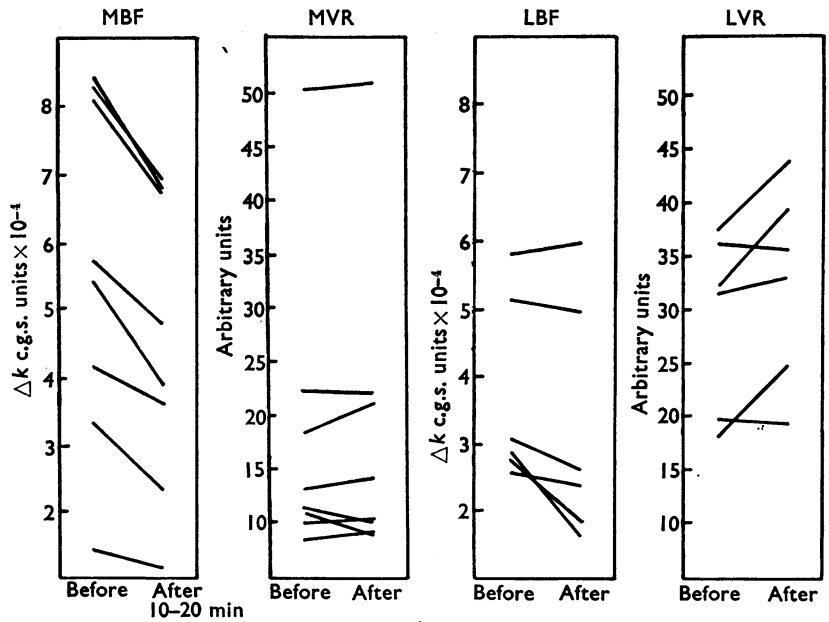


FIG. 3. Effect of alprenolol on myocardial blood flow (as myocardial thermal conductivity increment, Δk, c.g.s. units $\times 10^{-4}$), myocardial vascular resistance (arterial diastolic blood pressure mm Hg/thermal Δk) and on liver blood flow (as thermal conductivity increment, Δk, c.g.s. units $\times 10^{-4}$) and vascular resistance (mean blood pressure/Δk). The values are those before and 10–20 min after an intravenous injection of alprenolol (1·0 mg/kg).

to 109 ± 7 mm Hg with 1·0 mg/kg of the drug. LVEDP rose (6·6 ± 1 to 7·7 ± 0·8 mm Hg with 0·5 mg/kg; 5·7 ± 1·1 to 7·3 ± 0·9 mm Hg with 1·0 mg/kg alprenolol) significantly ($P<0·02$; $<0·02$) and this, together with the decreased +ve dp/dt, is clearly indicative of a decreased myocardial contractility induced by these amounts of alprenolol.

Right atrial pressure was unchanged by either dose of alprenolol, but the P-R interval was prolonged by a mean of 4 msec (range 3–10 msec).

Effect of alprenolol on myocardial blood flow, vascular resistance and metabolic heat production

The resting thermal conductivity increment (Δk) of the cat myocardium was found to vary between 1·4 and 9·0 c.g.s. units $\times 10^{-4}$, with a mean value of 5·5 units. This

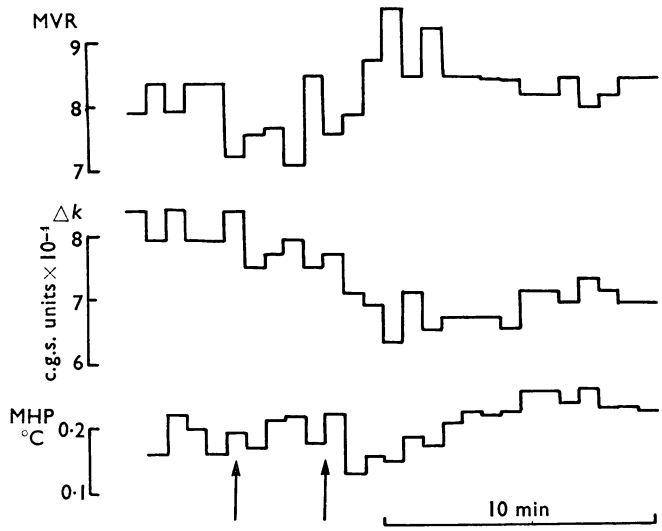


FIG. 4. Changes (from above) in myocardial vascular resistance, myocardial blood flow and myocardial metabolic heat production (°C) before and after two injections of alprenolol (0·5 mg/kg at the arrows). There is a reduction in blood flow and a transient increase in vascular resistance. Metabolic heat production is initially slightly depressed but recovers within 10 min.

TABLE 2. *Effect of alprenolol on metabolic heat production ("corrected temperature," °C) in the myocardium and in the liver*

Experiment	Myocardium Alprenolol (mg/kg)		Liver Alprenolol (mg/kg)
	0·5	1·0	1·0
1	+0·04	+0·02	No change
2	−0·05	No change	+0·03
3	+0·03	−0·03	−0·02
4	+0·05	−0·01	+0·01
5	No change	+0·01	+0·03
6	+0·04	+0·17	+0·06
7	−0·16	−0·05	
8	+0·09	+0·08	
Mean	< −0·01	+0·02	+0·02

large variation in resting blood flow between one experiment and another was probably due to differences in the depth of insertion of the recorder. It is known that there are gradients of blood flow across the ventricular wall (Kirk & Honig, 1964) resulting from the fact that the extra-vascular compression is greatest in the deepest (endocardial) regions. The mean value of myocardial thermal conductivity increment in these experiments was similar to that found in another series of cats anaesthetized with pentobarbitone sodium (McInnes & Parratt, 1969) and to that found in the dog, monkey and baboon (Parratt, 1969).

Table 1 summarizes the effect of a dose of 0·5 mg/kg alprenolol injected intravenously on myocardial thermal conductivity (Δk, an index of blood flow) and on calculated myocardial vascular resistance (diastolic aortic blood pressure mm Hg/Δk in c.g.s. units $\times 10^{-4}$) in eight cats. The mean decrease in flow was 11% and the myocardial vascular resistance was virtually unchanged. This means that the decrease in myocardial blood flow can be accounted for by the decrease in systemic pressure. The effect of alprenolol 1·0 mg/kg on myocardial blood flow and resistance are summarized in Fig. 3 and illustrated for one experiment in Fig. 4. The mean fall in myocardial blood flow was 17% (from 5·6 to 4·66 c.g.s. units $\times 10^{-4}$) and once again the mean effect on vascular resistance was negligible (18·00 to 18·22 arbitrary resistance units). Alprenolol had no consistent effect, in either dose, on

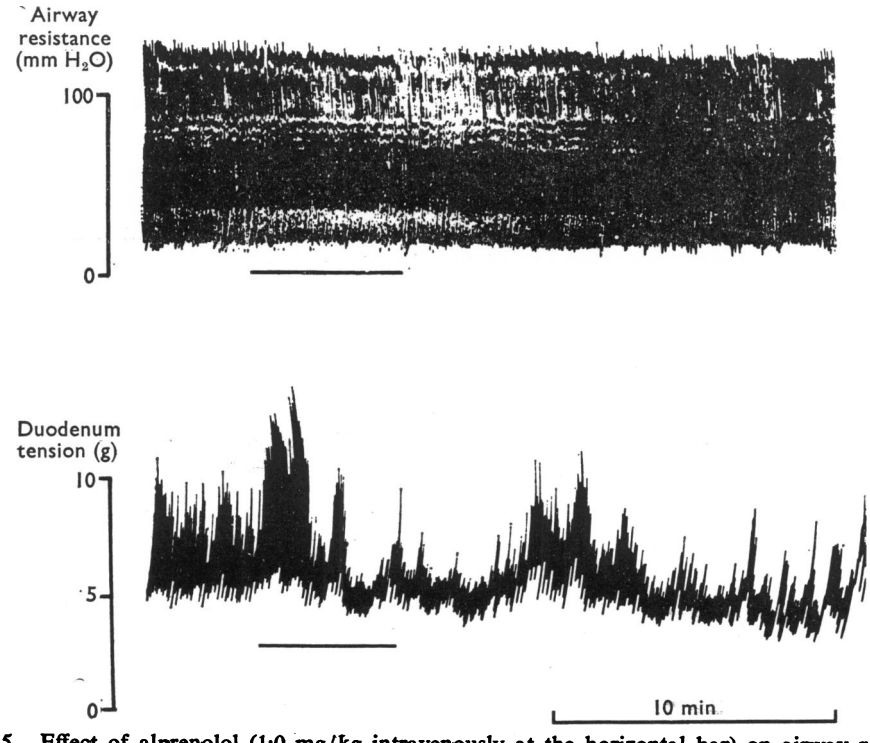


FIG. 5. Effect of alprenolol (1·0 mg/kg intravenously at the horizontal bar) on airway resistance (mm H_2O above) and on jejunal movement (measured with a strain gauge). Airway resistance is unaffected but there is initial stimulation of intestinal movement followed by a prolonged reduction in both spontaneous movement and in tone. Time scale 10 min.

calculated myocardial metabolic heat production (Table 2); in some experiments there was a slight rise (perhaps indicative of a β-stimulant action), in others a slight fall. The mean change ($< -0{\cdot}01°$ and $+0{\cdot}02°$ C) is not significant.

Effect of alprenolol on liver blood flow, vascular resistance and metabolic heat production

The mean thermal conductivity increment for liver was 3·7 c.g.s. units $\times 10^{-4}$. This means that resting liver blood flow is somewhat lower than that of the myocardium but is very similar to liver blood flow in the anaesthetized rat (Grayson & Kinnear (1958) quote a mean Δk value of 3·4 c.g.s. units $\times 10^{-4}$). Alprenolol decreased liver blood flow by about 15% (0·45 c.g.s. units $\times 10^{-4}$), which is similar to the effect on myocardial flow, and vascular resistance was slightly increased (from a mean of 29·1 to 32·6 resistance units). Alprenolol had no significant effect on liver metabolic heat production (Table 2).

Effect of alprenolol on extra-vascular smooth muscle

In five out of the twelve experiments in which intestinal movement was recorded, alprenolol decreased both tone and motility. This was occasionally preceded by stimulation (Fig. 5). Both tone and motility remained depressed for from ten to twenty minutes after the injection. In neither dose (fifteen experiments) did alprenolol influence airway resistance (Fig. 5).

Discussion

In doses which markedly reduced or abolished the myocardial stimulant effects of infused catecholamines (Parratt & Wadsworth, unpublished), alprenolol had very little effect on myocardial blood flow. Using an open-chest dog preparation, Ek & Åblad (personal communication, 1969) have shown that with a dose which in this preparation was sufficient to abolish the effects of cardiac sympathetic nerve stimulation, alprenolol had no effect on left coronary flow (measured with an electromagnetic flowmeter), coronary vascular resistance or on left ventricular contractile force and oxygen consumption. The absence of an effect on myocardial vascular resistance is in contrast to propranolol, which can markedly increase resistance to flow in the myocardium. Thus Parratt & Grayson (1966), using a heated thermocouple technique to measure myocardial blood flow in dogs, calculated that the mean increase in myocardial vascular resistance following a blocking dose of propranolol was 42%. One would naturally expect a decrease in myocardial blood flow after the administration of any drug which blocked myocardial β_1-receptors, in view of the known relationship between heart rate, myocardial contractile force, myocardial oxygen consumption and coronary blood flow (Feinberg, Katz & Boyd, 1962; Sonnenblick, Ross & Braunwald, 1968). There are good reasons, however, for believing that the decrease in myocardial blood flow that follows administration of propranolol is due partly to blockade of coronary vascular β_2-receptors (Parratt, 1967a, b) and partly to a "non-specific" action of propranolol unrelated to β-blockade (Whitsitt & Lucchesi, 1967). One would have expected that, in the present experiments, alprenolol would also have reduced myocardial blood flow, because there were quite marked reductions in heart rate and in the rate of rise of ventricular pressure. The fact that this was not so can be explained either on the basis of a

selective β_1-receptor blocking effect which is unlikely according to our own evidence (Parratt & Wadsworth, unpublished) or to that of Åblad *et al.* (1967) or on the basis of a partial degree of β-adrenoceptor stimulation. This latter explanation seems more reasonable and would account for the fact that, with the smaller dose of alprenolol, myocardial blood flow was sometimes increased (Table 1). Whatever the explanation, alprenolol, is a β-receptor blocking drug which reduces calculated myocardial oxygen consumption, reduces the myocardial and metabolic heat production stimulant actions of catecholamines (Åblad *et al.*, 1967 ; Parratt & Wadsworth, unpublished) and yet has no significant effect on myocardial vascular resistance. One would theoretically expect, therefore, that this would be a useful drug in the therapy of angina pectoris, and preliminary reports (Björntorp, 1967 ; 1968) show that this is likely.

There were, however, two experiments in which alprenolol quite markedly reduced myocardial blood flow (Table 1, experiments No. 17/01 and 11/04) and increased vascular resistance. In both cases it is interesting to note that the resting myocardial blood flow was low. A similar effect has been noted in one of a small series of monkey and baboon experiments (Parratt, 1969), where local flow around the implanted thermocouple recorder was reduced by propranolol to near zero levels. This again raises the question of the possible clinical danger of β-receptor blocking drugs. In situations of reduced myocardial irrigation (where probably the vessels of the microcirculation are already maximally dilated) a further reduction in perfusion pressure, such as might follow the administration of a β-receptor blocking drug, could well have serious consequences. It is possible that this is one factor in cases of cardiac failure precipitated by this type of drug. It would clearly be more likely to happen with propranolol than with alprenolol.

As in the myocardium, alprenolol had little effect on vascular resistance in the liver. This is again in marked contrast to propranolol, which Scholtholt, Lochner, Renn & Shiraishi (1967) have shown reduces canine hepatic arterial blood flow by from 18 to 38%.

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