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The effect of "selective" β-adrenoceptor blocking drugs on the myocardial circulation

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Summary

1. A comparison has been made of the effects of a relatively specific β_1-adrenoceptor blocking drug (practolol) and a relatively specific β_2-adrenoceptor blocking drug (butoxamine) on myocardial and general haemodynamics in anaesthetized cats.

2. Practolol, in a dose (10 mg/kg, intravenously) which had little effect on arterial pressure, heart rate, myocardial blood flow or myocardial vascular resistance, markedly reduced the effects of isoprenaline infusions on heart rate, aortic dp/dt, myocardial blood flow, vascular resistance and metabolic heat production, and the cardiac effort index. Isoprenaline induced vasodepression was unaffected.

3. Butoxamine (5 mg/kg, intravenously) decreased heart rate, aortic dp/dt, the cardiac effort index and myocardial blood flow and increased myocardial vascular resistance. This is taken as further evidence for the existence of β_2-adrenoceptors in the myocardial microcirculation.

4. After butoxamine, the effects of isoprenaline on myocardial blood flow, myocardial vascular resistance and heart rate were unaffected but the peripheral vasodilator effect was abolished. The effects on aortic dp/dt and the cardiac effort index were potentiated.

5. It is concluded that the effect of isoprenaline in increasing myocardial blood flow is due predominantly to increased cardiac work and oxygen consumption and that practolol, since it has little direct effect on myocardial blood flow yet abolishes the cardiac stimulant and oxygen wasting effects of released catecholamines, has properties which indicate that it should be an effective and safe anti-anginal drug.

Introduction

As a result of experiments with different β-adrenoceptor agonists and antagonists it has been suggested that β-adrenoceptors may be divided into sub-groups denoted β_1 and β_2 (Moran, 1966, 1967 ; Furchgott, 1967 ; Lands, Arnold, McAuliff, Luduena & Brown, 1967). Myocardial muscle β-adrenoceptors belong to the group classified as β_1, whereas β-adrenoceptors in the smooth muscle of the vascular bed, the intestine, the uterus and probably also of the bronchioles, belong to the β_2 group. Some antagonists (for example propranolol and sotalol) show little specificity and appear to block both types of adrenoceptor at similar dose levels. Other antagonists, the chemical structure of some of which is indicated in **Methods**, show

selectivity for one or other of the receptor types. Thus practolol [4-(2-hydroxy-3-isopropyl-aminopropoxy) acetanilide] is mainly active against myocardial (β_1) adrenoceptors (Barrett, Crowther, Dunlop, Shanks & Smith, 1967 ; Dunlop & Shanks, 1968) whereas butoxamine (N-tertiary butylmethoxamine) and its analogues, and also H 35/25 [1-(4′-methyl-phenyl)-2-isopropylaminopropanol] show more selectivity towards β_2-adrenoceptors (Levy, 1966a, 1966b ; Wilkenfeld & Levy, 1968 ; Levy & Wilkenfeld, 1969). This selectivity is not absolute, however, for large doses of practolol may block vascular as well as cardiac receptors (Barrett *et al.*, 1967) and large doses of butoxamine can antagonize the positive chronotropic effects of adrenaline in man (Hunninghake, Azarnoff & Waxman, 1966), in conscious dogs (Maxwell, Lindsay, Chaplin & Stilton, 1967) and in isolated atria (Maxwell *et al.*, 1967). Alprenolol [1-(*o*-allylphenoxy)-3-isopropylamino-2-propanol, H 56/28] initially blocks both types of receptor but recovery from blockade of β_1-adrenoceptors (in the myocardium) is faster than from blockade of β_2-adrenoceptors (in the vascular bed ; Parratt & Wadsworth, 1970).

One of the main uses of β-adrenoceptor blocking drugs is in the treatment of angina pectoris and the clinical value of propranolol in this condition has been especially well documented (see Fitzgerald, 1969). It is a valuable drug, acting by reducing the oxygen needs of the myocardium and perhaps also by antagonizing the myocardial calorigenic (or " oxygen wasting ") effects of released catecholamines (Shanks, 1967 ; Parratt, 1969). It has the disadvantages, however, that it also abolishes coronary autoregulation, decreases myocardial blood flow and increases myocardial vascular resistance (Parratt & Grayson, 1966a). These effects on flow and resistance are partly the result of decreased myocardial oxygen demand, but there is evidence that they also result from blockade of myocardial vascular β-adrenoceptors (Parratt & Grayson, 1966a, 1966b ; Parratt, 1967). If this is so, then clearly a β-adrenoceptor blocking drug with a selective action on myocardial (β_1) adrenoceptors should be clinically preferable. Such a drug would also enable the relative importance of the direct (vascular) and indirect (myocardial) effects of propranolol in reducing myocardial blood flow to be clarified. In the present study a comparison has been made of the effects of a relatively selective β_1-adrenoceptor antagonist (practolol) and a relatively selective β_2-adrenoceptor antagonist (butoxamine) on myocardial blood flow and on the cardiovascular responses to infused isoprenaline. A preliminary account of some of our findings has been communicated to the British Pharmacological Society (Parratt & Wadsworth, 1969).

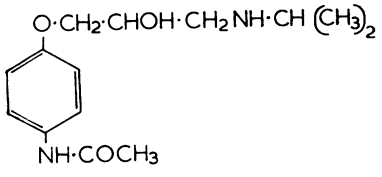
Methods

Cats were anaesthetized with sodium pentobarbitone (30 mg/kg by intraperitoneal injection) and ventilated with room air using a Palmer pump. The respiratory stroke volume (usually 40–60 ml ; rate 20/min) was adjusted to give an arterial pO_2 between 80 and 100 mmHg (1 mmHg≡1·333 mbar). Body temperature was maintained between 36·5° and 38° C and was measured by direct recording thermocouples from the rectum and the mid-oesophagus.

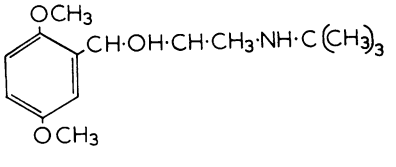
Blood flow in the muscle of the left myocardium was measured using the heated thermocouple method devised by Grayson (Grayson & Mendel, 1961 ; Grayson & Parratt, 1966). Details of the operational technique and of the calculations for measuring myocardial thermal conductivity increment, Δk (an index of blood flow around the implanted recorder) and assessing " corrected temperature " (an index

of metabolic heat production) have been described in full in previous publications (Dosekun, Grayson & Mendel, 1960 ; Grayson & Parratt, 1966 ; McInnes & Parratt, 1969).

Arterial systemic blood pressure was recorded from the descending aorta by means of a catheter (inserted via the left femoral artery) and a capacitance transducer (Elema-Schönander type EMT 35). Mean pressure was obtained by integration. As in a previous study (Parratt & Wadsworth, 1970), the rate of rise of the aortic pressure pulse with time (aortic dp/dt) was continuously determined with an analogue differentiator circuit in order to give indications of changes in peak aortic blood flow (Greenfield, Patel, Barnett & Fox, 1962). The cardiac effort index was calculated from the product of the heart rate and systolic arterial pressure (Robinson, 1967). Aortic pressure, aortic dp/dt, and the e.c.g. (lead II) were recorded on an Elema-Schönander recorder (Mingograph 81). Resting heart rate, arterial pressure and aortic dp/dt were measured before infusions of isoprenaline ((0·1–0·2 μg base/kg)/min for 5–10 min) and, from the continuous record taken during the infusion, the mean value of each parameter during the steady state period was estimated (Parratt & Wadsworth, 1970). The blocking drugs used were butoxamine (N-tertiary butylmethoxamine ; Burroughs Wellcome) and practolol [I.C.I. 50172 ; 4-(2-hydroxy-3-isopropyl-aminopropoxy) acetanilide ; Imperial Chemical Industries] ; (−)-isoprenaline bitartrate was obtained from J. Wyeth Ltd. All the results, in the text and in the tables, are expressed as means ± S.E. of the mean.



Practolol



Butoxamine

Results

Selectivity of β-blockade

Changes in heart rate and diastolic blood pressure produced by isoprenaline infusions were used as criteria for assessing the degree and specificity of β-blockade after the administration of butoxamine or practolol. After preliminary observations with lower doses of the two blocking drugs, we concluded that butoxamine, in a dose of 5 mg/kg intravenously, largely or completely prevented the fall in diastolic pressure without reducing isoprenaline induced tachycardia (selective blockade of β_2-adrenoceptors) whereas practolol, in a dose of 10 mg/kg intravenously, generally produced more than a 50% block of isoprenaline induced tachycardia without reducing the effect on diastolic blood pressure (selective blockade of β_1-adrenoceptors). The results described in this paper are taken from experiments in a total of twenty-three cats where, based on these criteria, butoxamine and practolol produced selective β_2- and selective β_1-blockade respectively.

Direct cardiovascular effects of practolol

In agreement with the results of Dunlop & Shanks (1968) selective β_1-adrenoceptor blocking doses of practolol produced only a slight, though significant, reduction in the resting heart rate (mean decrease, ± S.E. of mean, 10 ± 4

beats/min ; $P<0.05$). This is considerably less than the fall in heart rate produced by equivalent blocking doses of propranolol or of alprenolol (Parratt & Wadsworth, 1969). Practolol produced slight (but not significant) reductions in aortic dp/dt, cardiac output and in the calculated cardiac effort index. It had no effect on systemic arterial blood pressure, myocardial metabolic heat production (mean change $+0.01° \pm 0.02°$ C), myocardial blood flow or myocardial vascular resistance (Table 1, Fig. 1). The effect of a single injection of practolol on myocardial flow, resistance and heat production in one animal is illustrated in Fig. 2.

Effect of practolol on the cardiovascular effects of isoprenaline

The results are summarized in Table 2 and in Figs. 3, 4 and 5.

TABLE 1. *Effect of practolol (10 mg/kg) intravenously) on general and myocardial haemodynamics in cats*

	Control	After practolol
Mean blood pressure (mmHg)	117±5	119±4
Systolic blood pressure (SP) (mmHg)	152±5	153±5
Diastolic blood pressure (mmHg)	89±5	92±3
Heart rate (HR) (beats/min)	172±9	163±9*
Aortic dp/dt (mmHg/s)	2,350±260	2,170±250
Cardiac effort index ($SP \times HR \times 10^{-2}$)	265±21	251±18
Myocardial blood flow (MBF) (conductivity increment, Δk, c.g.s. units $\times 10^{-4}$)	5·1±0·6†	5·0±0·6
Myocardial vascular resistance (diastolic blood pressure/MBF; arbitary units)	19·3±1·9	21·2±1·7

* Significantly different from controls at a level of $P<0.05$.
†=5·1±0·6×0·04187 Jm/m² s °C.

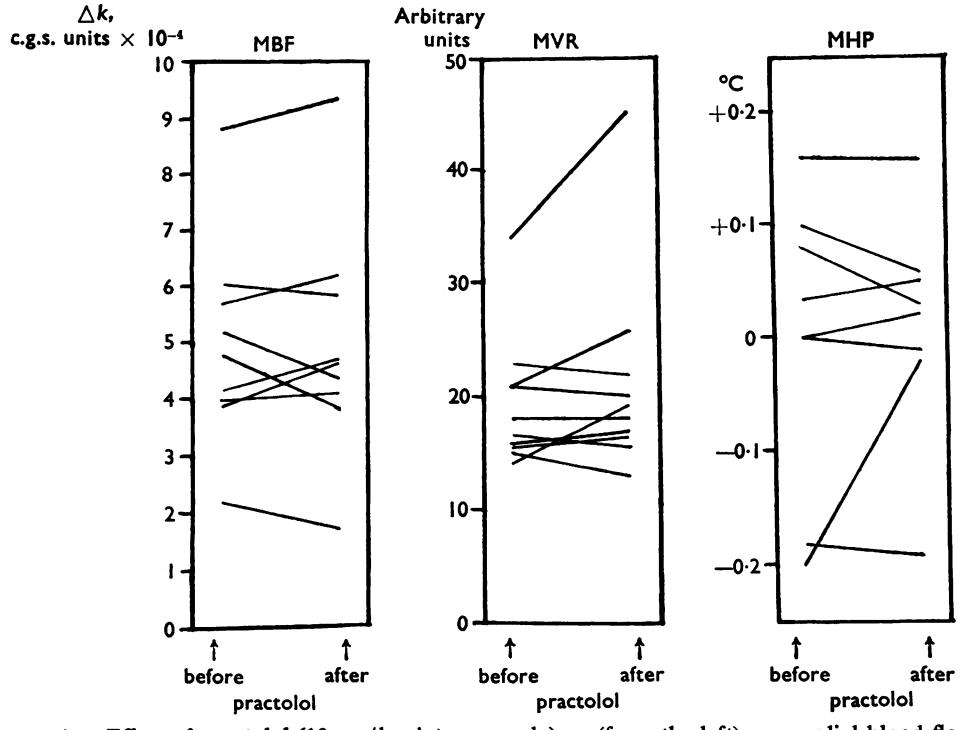


FIG. 1. Effect of practolol (10 mg/kg, intravenously) on (from the left) myocardial blood flow (MBF, as myocardial thermal conductivity increment, Δk, c.g.s. units $\times 10^{-4}$), myocardial vascular resistance (MVR, diastolic arterial pressure/myocardial thermal conductivity increment, arbitary units) and myocardial metabolic heat production (MHP, as "corrected temperature", ° C) in anaesthetized cats.

Effects on heart rate and diastolic blood pressure

Infusions of isoprenaline increased heart rate by 48±6 beats/min before, and by 19±3 beats/min after, practolol. This inhibition of isoprenaline induced tachycardia was significant ($P<0.001$) and represents a 61% block of the myocardial (β_1) response. Isoprenaline infusions reduced diastolic arterial pressure by 9±2

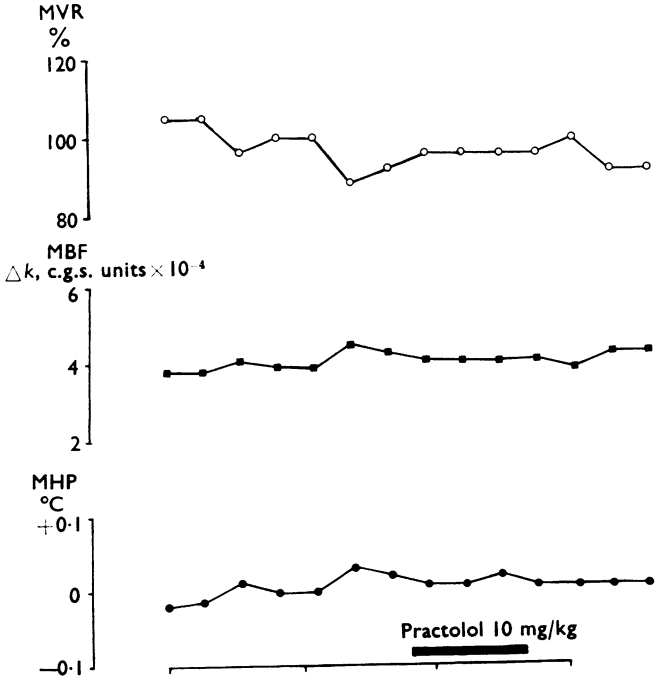


FIG. 2. Effect of a single injection of practolol (10 mg/kg at the solid bar) on (from above) myocardial vascular resistance (MVR, % of pre-injection level), myocardial blood flow (MBF, as myocardial thermal conductivity increment, Δk) and myocardial metabolic heat production (MHP, as "corrected temperature", ° C) in an anaesthetized cat. Time scale, 5 min.

TABLE 2. *Effect of isoprenaline infusions on general and myocardial haemodynamics before and after practolol (10 mg/kg intravenously)*

	Before practolol		After practolol	
	Control	Isoprenaline	Control	Isoprenaline
Systolic blood pressure (SP) (mmHg)	152±5	162±5	154±3	156±4**
Diastolic blood pressure (mmHg)	92±4	80±4	91±3	79±4
Heart rate (HR) (beats/min)	169±9	218±10	163±8	182±8*
Aortic dp/dt (mmHg/s)	2,060±270	3,250±270	2,210±230	2,950±290***
Cardiac effort index ($SP \times HR \times 10^{-2}$)	253±23	341±22	251±16	280±16*
Myocardial blood flow (MBF) (conductivity increment, Δk, c.g.s. units $\times 10^{-4}$)	4·2±0·4	6·9±0·8	5·0±0·5	5·7±0·4**
Myocardial vascular resistance (diastolic blood pressure/MBF)	25·5±3·5	12·7±1·1	20·6±2·5	15·1±1·1**

Isoprenaline response after practolol significantly different from control isoprenaline response at a level of * $P<0.001$; ** $P<0.01$; *** $P<0.02$.

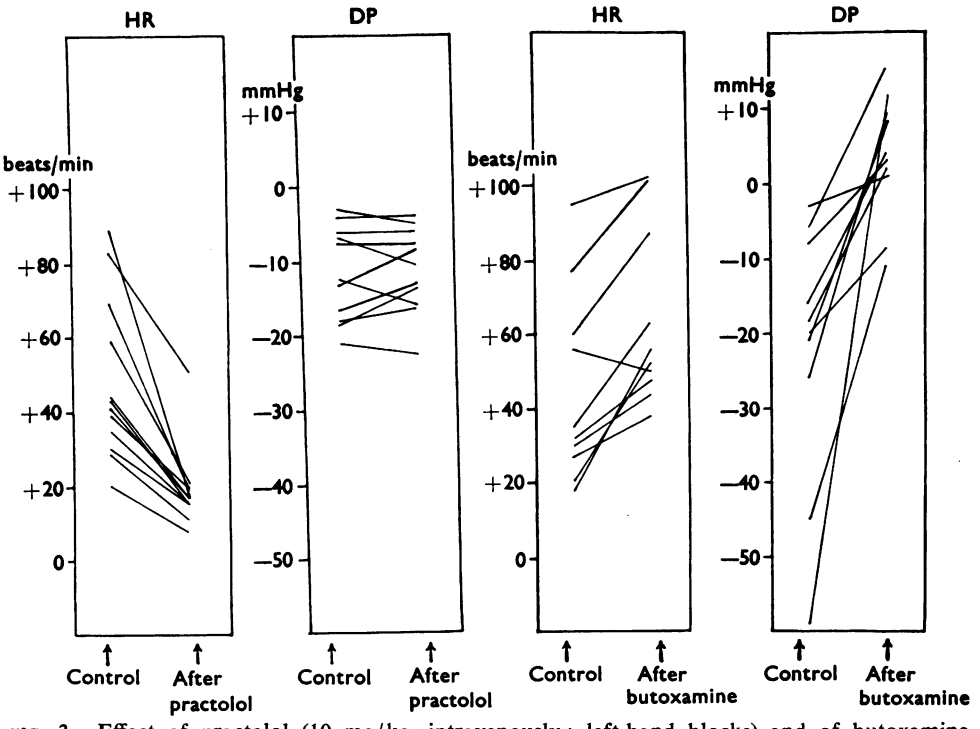


FIG. 3. Effect of practolol (10 mg/kg, intravenously; left-hand blocks) and of butoxamine (5 mg/kg, intravenously; right-hand blocks) on the changes in heart rate (HR, beats/min) and in diastolic blood pressure (DP, mmHg) induced by infusions of isoprenaline ((0·25 μg/kg)/min).

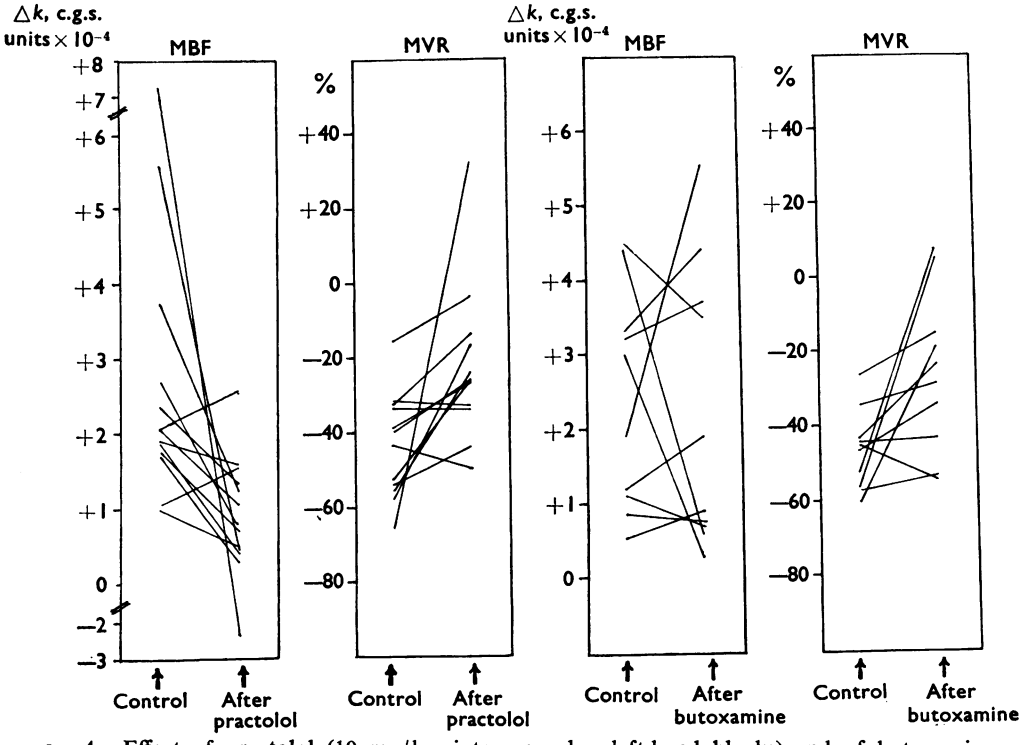


FIG. 4. Effect of practolol (10 mg/kg, intravenously; left-hand blocks) and of butoxamine (5 mg/kg, intravenously; right-hand blocks) on the changes in myocardial blood flow (MBF, as Δk, c.g.s. units $\times 10^{-4}$) and in myocardial vascular resistance (MVR, % of pre-infusion value) induced by intravenous infusions of isoprenaline ((0·25 μg/kg)/min).

mmHg before and by 11 ± 2 mmHg after practolol ; this difference is not significant ($P > 0{\cdot}4$) and is indicative that vascular β_2-adrenoceptors were not blocked.

Effects on myocardial blood flow, vascular resistance and heat production

Control infusions of isoprenaline increased myocardial blood flow by 64% before practolol and by 14% after it. Calculated myocardial vascular resistance was reduced by isoprenaline by 44 ± 4% before practolol and by 22 ± 5% after practolol. Thus practolol produced a 49% block of the isoprenaline induced myocardial vascular resistance change. This is illustrated in Fig. 6.

Control infusions of isoprenaline increased myocardial " corrected temperature " by $0{\cdot}07° \pm 0{\cdot}02°$ C. This temperature increase represents the change in myocardial metabolism which isoprenaline produces, partly as a result of increased cardiac work and partly as a result of " oxygen wastage " by the myocardium (Parratt, 1969 ; Parratt & Wadsworth, 1970). This isoprenaline induced increase in myocardial heat

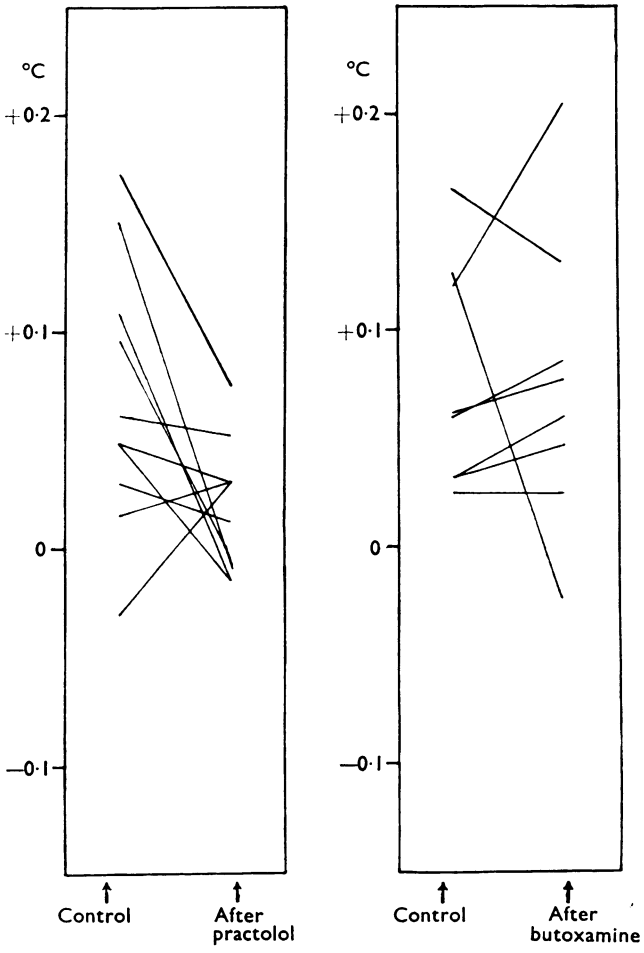


FIG. 5. Effect of practolol (10 mg/kg intravenously ; left-hand block) and of butoxamine (5 mg/kg intravenously ; right-hand block) on the changes in myocardial metabolic heat production (as " corrected temperature ", °C) induced by intravenous infusions of isoprenaline ((0·25 μg/kg)/min).

production was significantly reduced ($P<0.05$) by the previous administration of practolol (see Figs. 5 and 6).

Other haemodynamic effects

Isoprenaline increased aortic dp/dt by $68 \pm 12\%$ and calculated cardiac output by $119 \pm 21\%$. These effects were considerably reduced after partial blockade of myo-

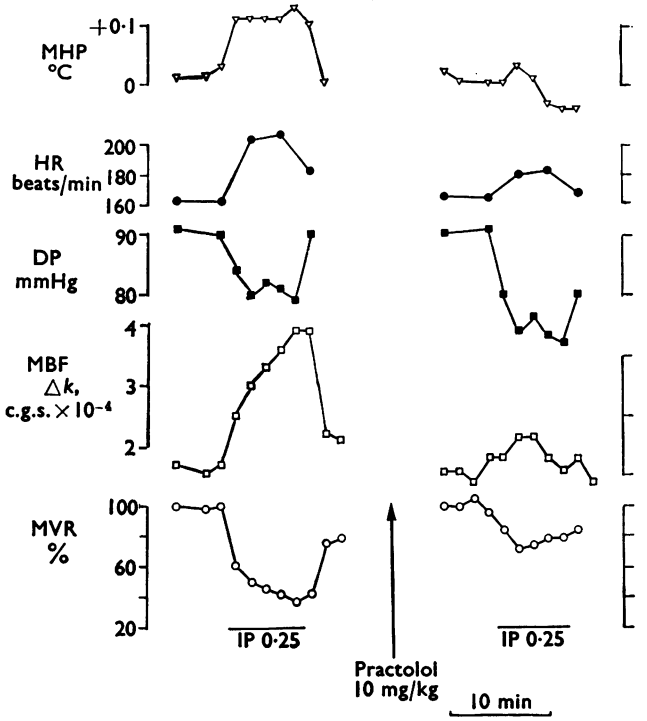


FIG. 6. Effect of intravenous infusions of isoprenaline (IP, 0·25 μg/kg per min, at the horizontal bars) on (from above) metabolic heat production (MHP, as " corrected temperture ", °C), heart rate (HR, beats/min), diastolic blood pressure (DP, mmHg), myocardial blood flow (MBF, as myocardial thermal conductivity increment, Δk) and myocardial vascular resistance (MVR, % of pre-infusion levels) before (on the left) and after (on the right) an intravenous injection of practolol (10 mg/kg at the arrow).

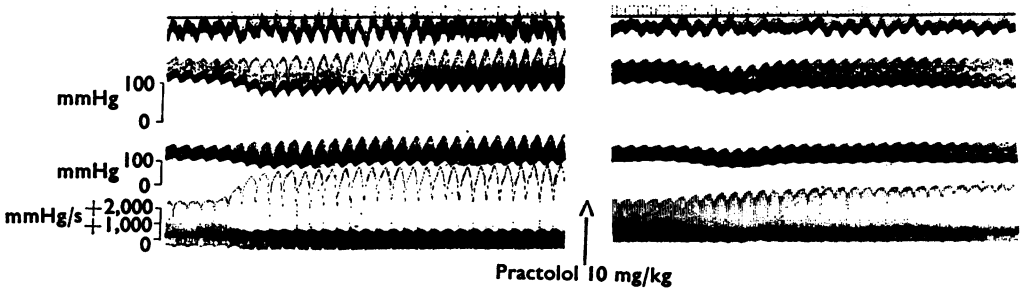


FIG. 7. Effect of isoprenaline infusions ((0·25 μg/kg)/min) starting 30 s before the start of each panel) on (from above) the electrocardiogram, femoral arterial pressure (mmHg), descending aortic pressure (mmHg) and aortic dp/dt (mmHg/s) before (on the left) and after (on the right) an intravenous injection of practolol (10 mg/kg). The vasodepressor effect of isoprenaline is largely unaltered by practolol but there is a marked reduction in the effect on aortic dp/dt. Top trace, time scale 1 s.

cardial β_1-adrenoceptors (see Fig. 7). Thus, after practolol, similar infusions of isoprenaline increased aortic dp/dt by $35 \pm 6\%$ and calculated cardiac output by $51 \pm 8\%$ (differences significant at levels of $P<0{\cdot}025$ and $<0{\cdot}01$ respectively). The cardiac effort index was increased by control infusions of isoprenaline (mean change $+39 \pm 6\%$) and again, this effect was much less after practolol (mean change $+12 \pm 3\%$). The isoprenaline-induced increase in systolic arterial pressure was abolished by practolol (see Table 2).

Direct cardiovascular effects of butoxamine

The results are summarized in Table 3 and in Fig. 8.

In doses which selectively blocked β_2-adrenoceptors, butoxamine reduced heart rate and aortic dp/dt; consequently cardiac output also decreased (by $36 \pm 15\%$). The cardiac effort index was also reduced (by $15 \pm 4\%$). After butoxamine,

TABLE 3. *Effect of butoxamine (5 mg/kg, intravenously) on general and myocardial haemodynamics in cats*

	Control	After butoxamine
Mean blood pressure (mmHg)	111±7	114±8
Systolic blood pressure (SP) (mmHg)	155±9	149±8
Diastolic blood pressure (mmHg)	89±7	93±8
Heart rate (HR) (beats/min)	229±12	200±12*
Aortic dp/dt (mmHg/s)	3,380±350	2,420±240*
Cardiac effort index ($SP \times HR \times 10^{-2}$)	359±35	302±31**
Myocardial blood flow (MBF) (conductivity increment, Δk, c.g.s. units $\times 10^{-4}$)	7·5±2·8	6·6±2·8**
Myocardial vascular resistance (diastolic blood pressure/MBF; arbitrary units)	23±8	31±12

Significantly different from controls at levels of * $P<0{\cdot}001$; ** $P<0{\cdot}01$.

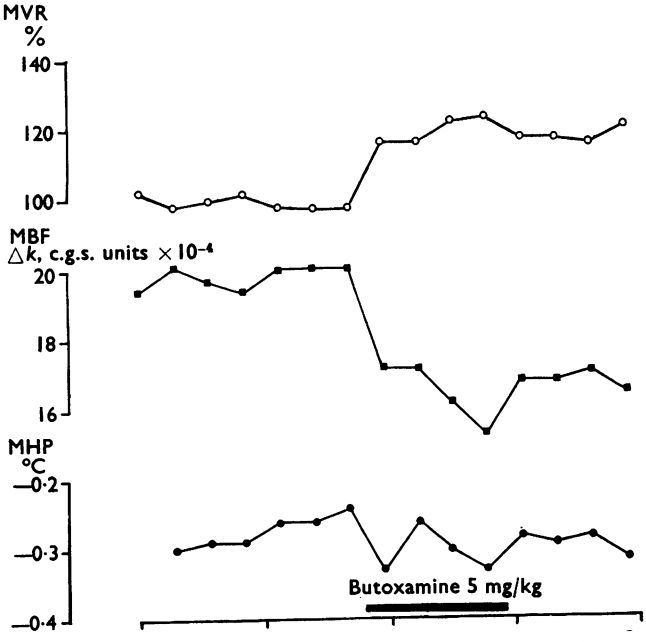


FIG. 8. Effect of butoxamine (5 mg/kg, intravenously; at the solid bar) on (from above) myocardial vascular resistance (MVR, % of pre-injection level), myocardial blood flow (MBF, as myocardial thermal conductivity increment, Δk, c.g.s. units $\times 10^{-4}$) and on metabolic heat production (MHP, as "corrected temperature", ° C). Time scale, 5 min.

myocardial vascular resistance increased by 33±6% and myocardial blood flow decreased by 20±7%. Butoxamine had no consistent effect on myocardial metabolic heat production.

Despite the fact that butoxamine, in a dose of 5 mg/kg, blocked the effects of isoprenaline on vascular (β_2) receptors, it had no significant direct effect on diastolic or systolic aortic pressures although the pulse pressure was reduced (mean change 11±3 mmHg), presumably the result of diminished cardiac output. The effect of an injection of butoxamine on the arterial blood pressure and on aortic dp/dt is illustrated in Fig. 9.

Effect of butoxamine on the cardiovascular effects of isoprenaline

These results are summarized in Table 4 and in Figs 3, 4 and 5.

Effects on heart rate and diastolic blood pressure

Control infusions of isoprenaline lowered aortic diastolic pressure by 22±6 mmHg. Similar infusions after butoxamine (5 mg/kg) produced a slight but not significant increase in diastolic pressure (mean increase 3±3 mmHg).

In contrast, isoprenaline tachycardia was unaffected by butoxamine. This increase in heart rate produced by isoprenaline after butoxamine was in fact significantly greater ($P<0.02$) than the increase produced by the control infusions, although the peak value attained during the isoprenaline infusions was similar in each case. Thus before butoxamine isoprenaline increased the heart rate from a mean of 231 to 276 beats/min and after butoxamine from 199 to 263 beats/min.

Effects on myocardial blood flow, vascular resistance and metabolic heat production

Infusions of isoprenaline increased myocardial blood flow to the same extent before and after butoxamine. Calculated myocardial vascular resistance was always

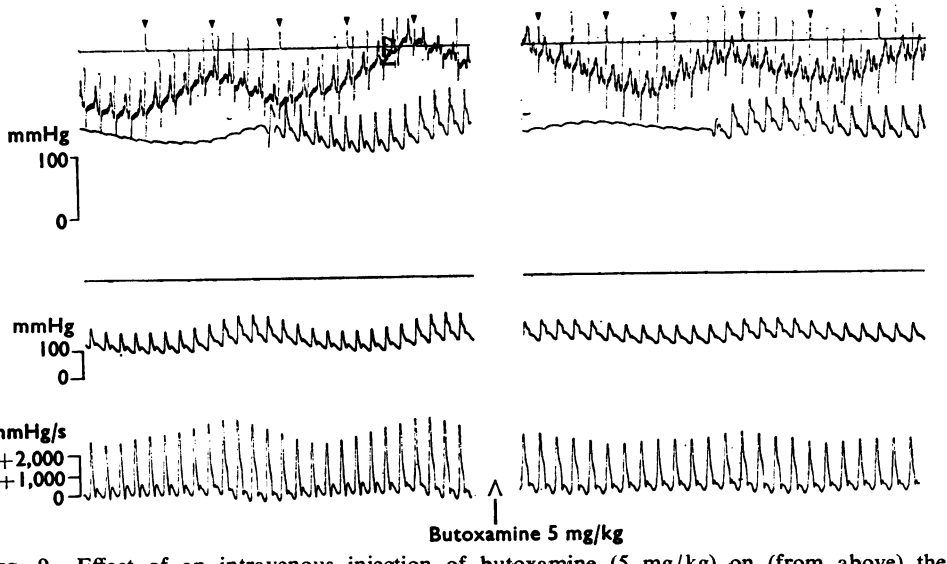


FIG. 9. Effect of an intravenous injection of butoxamine (5 mg/kg) on (from above) the electrocardiogram (lead II), femoral arterial pressure (mmHg ; initially integrated), descending aortic pressure (mmHg) and aortic dp/dt (mmHg/s) of an anaesthetized cat. On the left before butoxamine ; on the right after butoxamine. There is marked bradycardia, a reduction in aortic dp/dt but no significant change in mean arterial pressure. Time scale 1 s marks (▼).

considerably reduced by control infusions of isoprenaline (mean decrease $46 \pm 3\%$). In some experiments this effect was not affected by the previous administration of butoxamine, whilst in others it was, by varying amounts (see Fig. 4). The mean decrease in myocardial vascular resistance with isoprenaline after butoxamine was $25 \pm 7\%$, which is significantly less than the control isoprenaline response ($P<0{\cdot}02$).

Infusions of isoprenaline increased myocardial "corrected temperature" to the same extent ($0{\cdot}08° \pm 0{\cdot}02°$ C) both before and after butoxamine.

Other haemodynamic effects

Isoprenaline infusions increased aortic dp/dt by $81 \pm 13\%$, calculated cardiac output by $126 \pm 22\%$ and the cardiac effort index by $29 \pm 6\%$. Similar infusions after butoxamine increased aortic dp/dt by $110 \pm 19\%$, cardiac output by $191 \pm 28\%$ and the cardiac effort index by $68 \pm 10\%$. Thus butoxamine significantly ($P<0{\cdot}005$) augmented those effects of isoprenaline which involve cardiac (β_1) adrenoceptors.

Discussion

This study demonstrates that isoprenaline increases myocardial blood flow through two mechanisms: first, and predominantly, as a result of increased cardiac work (heart rate and contractility) and the concomitant increase in myocardial oxygen consumption; secondly, and much less important, as a result of a direct action on the myocardial vascular (β_2) adrenoceptors. The evidence for this is as follows. Practolol, in doses which markedly reduce the effects of isoprenaline on heart rate and dp/dt but which have no effect on isoprenaline induced vasodilatation, markedly reduces the effect of isoprenaline on myocardial blood flow. We made no attempt to block the myocardial stimulant effects of infused isoprenaline completely and it is likely that this accounts for the failure of practolol to antagonize completely the isoprenaline effect on myocardial blood flow and vascular resistance (Table 2). The experiments with butoxamine confirm this conclusion.

TABLE 4. *Effect of isoprenaline infusions on general and myocardial haemodynamics before and after butoxamine (5 mg/kg intravenously)*

	Before butoxamine		After butoxamine	
	Control	Isoprenaline	Control	Isoprenaline
Systolic blood pressure (SP) (mmHg)	148 ± 10	154 ± 10	141 ± 8	171 ± 10**
Diastolic blood pressure (mmHg)	95 ± 8	72 ± 6	93 ± 7	96 ± 6*
Heart rate (HR) (beats/min)	231 ± 14	276 ± 10	199 ± 11	263 ± 10***
Aortic dp/dt (mmHg/s)	$2{,}950 \pm 320$	$5{,}140 \pm 470$	$2{,}400 \pm 220$	$4{,}810 \pm 390$**
Cardiac effort index ($SP \times HR \times 10^{-2}$)	335 ± 38	419 ± 35	271 ± 27	441 ± 30**
Myocardial blood flow (MBF) (conductivity increment, c.g.s. units $\times 10^{-4}$)	$6{\cdot}7 \pm 2{\cdot}0$	$9{\cdot}1 \pm 2{\cdot}4$	$6{\cdot}7 \pm 1{\cdot}9$	$8{\cdot}9 \pm 2{\cdot}2$
Myocardial vascular resistance (diastolic blood pressure/MBF; arbitrary units)	29 ± 6	15 ± 3	27 ± 7	18 ± 4***

Isoprenaline response after butoxamine significantly different from control isoprenaline response at a level of * $P<0{\cdot}001$; ** $P<0{\cdot}01$; *** $P<0{\cdot}02$.

After butoxamine, in doses which abolished or reversed isoprenaline vasodepression (the β_2 effect), isoprenaline increased myocardial blood flow to the same extent as it did before β_2 blockade. The fact that butoxamine itself reduced myocardial blood flow and increased myocardial vascular resistance can be taken as evidence for the existence of myocardial (vascular) β_2-adrenoceptors. Both heart rate and aortic dp/dt were significantly reduced, so a direct myocardial depressant effect cannot be ruled out, but it is considered more likely that this myocardial depression was the result and not the cause of the myocardial vasoconstriction. A further conclusion can be drawn: that the mechanism through which increased cardiac work and oxygen consumption increase myocardial blood flow is not through activation of myocardial vascular (β_2) adrenoceptors.

In doses that considerably reduced the effects of isoprenaline on heart rate, aortic dp/dt, cardiac effort index and myocardial metabolic heat production, practolol had almost no effect on systemic arterial blood pressure or on myocardial blood flow (Table 1). Since the anti-anginal effect of the beta-adrenoceptor blocking drugs is probably determined by a reduction in the need of the myocardium for oxygen and by antagonism of the calorigenic effect of released catecholamines, properties exhibited by practolol, it is likely that this drug would be effective in this condition. Furthermore, we suggest that it would be preferable to drugs which block vascular, as well as myocardial, β-adrenoceptors. There is no evidence of coronary vasoconstriction with practolol and, because it is selective for myocardial (β_1) adrenoceptors, one would not expect it to interfere with coronary autoregulation as propranolol does (Parratt & Grayson, 1966a). These results with selective β-adrenoceptor blocking drugs in fact confirm a previous conclusion (Parratt & Grayson, 1966a, b) that propranolol decreases myocardial blood flow partly by reducing myocardial oxygen demands but also by blockade of myocardial vascular (β_2) adrenoceptors. Although this has yet to be determined, one would not expect the release of myocardial catecholamines to cause myocardial vasoconstriction in the presence of practolol as they do in the presence of propranolol (Gaal, Kattus, Kolin & Ross, 1966 ; Parratt, 1969).

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REFERENCES

BARRETT, A. M., CROWTHER, A. F., DUNLOP, D., SHANKS, R. G. & SMITH, L. H. (1967). Cardioselective β-blockade, *Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.*, **259**, 152.

DOSEKUN, F. O., GRAYSON, J. & MENDEL, D. (1960). The measurement of the metabolic and vascular responses in liver and muscle with observations on their responses to insulin and glucose. *J. Physiol., Lond.*, **150**, 581–606.

DUNLOP, D. & SHANKS, R. G. (1968). Selective blockade of adrenoceptive beta receptors in the heart. *Br. J. Pharmac. Chemother.*, **32**, 201–218.

FITZGERALD, J. D. (1969). Perspectives in adrenergic beta-receptor blockade. *Clin. Pharmac.*, **10**, 292–306.

FURCHGOTT, R. F. (1967). The pharmacological differentiation of adrenergic receptors. *Ann. N.Y. Acad. Sci.*, **139**, 553–570.

GAAL, P. G., KATTUS, A. A., KOLIN, A. & ROSS, G. (1966). Effects of adrenaline and noradrenaline on coronary blood flow before and after beta-adrenergic blockade. *Br. J. Pharmac. Chemother.*, **26**, 713–722.

GRAYSON, J. & MENDEL, D. (1961). Myocardial blood flow in the rabbit. *Am. J. Physiol.*, **200**, 968–974.

GRAYSON, J. & PARRATT, J. R. (1966). A species comparison of the effects of changing perfusion-pressure on blood flow and metabolic heat production in the myocardium. *J. Physiol., Lond.*, **187**, 465–488.

GREENFIELD, J. C., PATEL, D. J., BARNETT, G. O. & FOX, S. M. (1962). Evaluation of the pressure time derivative method for estimating peak blood flow. *Am. Heart J.*, **64**, 101–105.

HUNNINGHAKE, D. B., AZARNOFF, D. L. & WAXMAN, D. (1966). The effect of butoxamine on catecholamine-induced metabolic changes in humans. *Clin. Pharmac.*, **7**, 470–476.

LANDS, A. M., ARNOLD, A., MCAULIFF, J. P., LUDUENA, F. P. & BROWN, T. G. JR. (1967). Differentiation of receptor systems activated by sympathomimetic amines. *Nature, Lond.*, **215**, 597–598.

LEVY, B. (1966a). Adrenergic blocking activity of N-tertiary butylmethoxamine (butoxamine). *J. Pharmac. exp. Ther.*, **151**, 413–422.

LEVY B. (1966b). Dimethyl isopropylmethoxamine : a selective beta-receptor blocking agent. *Br. J. Pharmac. Chemother.*, **27**, 277–285.

LEVY, B. & WILKENFELD, B. E. (1969). An analysis of selective beta receptor blockade. *Eur. J. Pharmac.*, **5**, 227–234.

MAXWELL, R. A., LINDSAY, L. A., CHAPLIN, E. & STILTON, J. (1967). Butoxamine blockade of isoproterenol in the heart and vasculature of the dog. *Fedn. Proc.*, **26**, 402.

MCINNES, LINDA & PARRATT, J. R. (1969). Studies on the mode of action of hexobendine, a prospective anti-anginal drug. *Br. J. Pharmac.*, **37**, 272–282.

MORAN, N. C. (1966). Pharmacological characterization of adrenergic receptors. *Pharmac. Rev.*, **18**, 503–512.

MORAN, N. C. (1967). The development of beta adrenergic blocking drugs: a retrospective and prospective evaluation. *Ann. N.Y. Acad. Sci.*, **139**, 649–660.

PARRATT, J. R. (1967). The effect of adrenergic neurone blockade on the myocardial circulation. *Br. J. Pharmac. Chemother.*, **31**, 513–522.

PARRATT, J. R. (1969). The effect of adrenaline, noradrenaline and propranolol on myocardial blood flow and metabolic heat production in monkeys and baboons. *Cardiovasc. Res.*, **3**, 306–314.

PARRATT, J. R. & GRAYSON, J. (1966a). Myocardial vascular reactivity after beta-adrenergic blockade. *Lancet*, **1**, 338–340.

PARRATT, J. R. & GRAYSON, J. (1966b). Myocardial vascular reactivity. *Lancet*, **1**, 819.

PARRATT, J. R. & WADSWORTH, R. M. (1969). The effect of "selective" beta-receptor blocking drugs on the myocardial circulation. *Br. J. Pharmac.*, **37**, 524–526*P*.

PARRATT, J. R. & WADSWORTH, R. M. (1970). The effect of catecholamine infusions on myocardial blood flow, metabolic heat production and on general haemodynamics, before and after alprenolol (H 56/28), in anaesthetised cats. *Br. J. Pharmac.*, **38**, 554–571.

ROBINSON, B. F. (1967). Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation*, **35**, 1073–1083.

SHANKS, R. G. (1967). The sympathetic nervous system. In *Problems in Laboratory Evaluation of Antianginal Agents*, ed. Winbury, M. M., pp. 41–53. Amsterdam: North-Holland.

WILKENFELD, B. E. & LEVY, B. (1968). Adrenergic blocking properties of MJ 1999 and butoxamine on cardiac and vascular beta-receptors. *Archs int. Phamacodyn. Thér.*, **176**, 218–232.

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