*Br. J. Pharmac.* (1971), **42**, 193–204.

# Cardiovascular pharmacology of quazodine (MJ-1988), with particular reference to effects on myocardial blood flow and metabolic heat production

J. R. PARRATT AND EILEEN WINSLOW

*The Department of Pharmacology, University of Strathclyde, Glasgow C1*

## Summary

1. The effects of intravenous infusions of quazodine (6,7-dimethoxy-4-ethylquinazoline ; MJ-1988) on myocardial blood flow, myocardial metabolic heat production and on general haemodynamics have been studied in cats anaesthetized with sodium pentobarbitone.

2. Quazodine (0·25 and 0·5 (mg/kg)/min for 10 min) decreased diastolic blood pressure, peripheral vascular resistance, systolic ejection time and left ventricular end-diastolic pressure. Heart rate, cardiac effort, output and external work and left ventricular $dP/dt$ were markedly increased. These changes are indicative of increased myocardial contractility and peripheral vasodilatation.

3. In a dose of (1·0 mg/kg)/min, quazodine had a more marked hypotensive effect, systolic pressure being significantly reduced, and had less effect on left ventricular $dP/dt$ and cardiac effort. Calculated external cardiac work was slightly reduced and there were very occasional nodal arrhythmias.

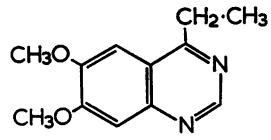
4. Changes in heart rate, aortic $dP/dt$ and diastolic blood pressure induced by quazodine were unaffected by the previous administration of the $\beta$-adrenoceptor blocking agent alprenolol in a dose (1·0 mg/kg) which abolished the effects of isoprenaline.

5. In all doses, quazodine markedly increased local blood flow (by 70–540%) around an implanted myocardial heated thermocouple recorder. ' Corrected temperature ', an index of local myocardial metabolic heat production, was almost unchanged and it is suggested that increased myocardial contractility, occurring with unchanged metabolic heat production and oxygen consumption, probably results from a concomitant decrease in intramural wall tension.

## Introduction

Quazodine (6,7-dimethoxy-4-ethylquinazoline ; MJ-1988) is a potent cardiac stimulant with bronchodilator and vasodilator properties (Lish, Cox, Dungan & Robbins, 1964 ; Aviado, Folle & Pisanty, 1967). Cardiac performance is improved in the dog heart-lung preparation and augmented myocardial contractility is accompanied by increased coronary blood flow and by pulmonary vasodilatation. Carr, Cooper, Daggett, Lish, Nugent & Powers (1967) showed that quazodine increased

left ventricular $dP/dt$ max and decreased both left ventricular end-diastolic pressure and the duration of systole in dogs on right heart bypass. Despite these changes, myocardial oxygen consumption was not increased. These cardiac effects were not antagonized by $\beta$-adrenoceptor blockade and could still be demonstrated in dogs subjected to chronic cardiac denervation. Carr and his colleagues concluded that quazodine has direct actions on cardiac and smooth muscle cells, and does not owe its effects to interaction with adrenoceptors, with release of stored catecholamines or with activation of cardiac autonomic reflexes.




Perhaps the most striking property of quazodine is its apparent ability to increase myocardial contractility without increasing myocardial oxygen consumption (Carr *et al.*, 1967). It is possible that this ' oxygen sparing effect ' is related to a reduction in metabolic waste heat produced by the myocardium which would result from a reduced intramyocardial wall tension. The purpose of our investigation was twofold. First, to examine in detail the general haemodynamic effects of quazodine and relate these changes to changes in myocardial metabolic heat production ; second, to determine its effect on local blood flow in the muscle of the left ventricle.

## Methods

Twenty-five cats of either sex and weighing 1·8–6·3 kg were anaesthetized with an intraperitoneal injection of sodium pentobarbitone (30 mg/kg). The animals were ventilated with room air by means of a Palmer pump, the respiratory stroke volume of which was adjusted such that after thoracotomy, the arterial $pO_2$ was between 75 and 100 mmHg (1 mmHg$\equiv$1·333 mbar). Rectal, mid-oesophageal and occasionally skeletal muscle, skin and arterial blood temperatures were measured using direct recording thermocouples (Ellab, Copenhagen).

Left ventricular systolic and end-diastolic pressures (LVSP ; LVEDP), left ventricular $dP/dt$ max, descending aortic $dP/dt$ max, heart rate, arterial pressure, right atrial pressure and the electrocardiogram (lead I or II) were recorded, as previously outlined (McInnes & Parratt, 1969 ; Parratt & Wadsworth, 1969) on an eight channel Elema-Schönander recorder (Mingograph 81). Systolic ejection time was measured from the beginning of the upstroke of the central aortic pressure pulse to the trough of the incisural notch.

Cardiac output was measured in some of the experiments using a thermal dilution technique (Hosie, 1962). A 36 s.w.g. copper-constantan junction was inserted by way of the right femoral artery into the descending aorta ; the cold (reference) junction, together with a direct recording thermocouple was in the rectum. The output from the thermocouple circuit was fed directly into a Kipp & Zonen BD5 recorder (50 $\mu$V for a full scale of 20 cm=1·2° C). The paper speed was 200 mm/minute. A bolus of 1 or 2 ml of saline at room temperature (18–24° C) was injected into the right atrium and the area under the thermodilution curve calculated by the method of Williams, O'Donovan & Wood (1966).

Blood flow in the muscle of the left myocardium was measured using a heated thermocouple technique (Grayson & Mendel, 1961 ; Grayson & Parratt, 1966). The recorder was implanted in the apical region of the myocardium and the output fed directly into a second Kipp and Zonen BD5 recorder (100 $\mu$V full scale of 20 cm= 2·5° C). The cold (reference) junction was positioned in the aortic arch via the left common carotid artery. Full experimental details and the methods of calculating myocardial thermal conductivity increment (which is an index of local blood flow around the recorder) and 'corrected temperature' (an index of myocardial metabolic heat production) have been described in previous publications (Grayson & Parratt, 1966 ; McInnes & Parratt, 1969 ; Parratt, 1969). In six experiments liver blood flow was measured using a similar heated thermocouple technique.

The following data were derived:

1. Myocardial vascular resistance (arbitrary units)
=diastolic arterial blood pressure (mmHg) (i.e. per) myocardial thermal conductivity increment ($\Delta$k ; as cal/cm s° C* $\times 10^{-4}$)

2. Cardiac effort index (Robinson, 1967)
=systolic blood pressure (mmHg) $\times$ heart rate (beats/min) $\times 10^{-2}$

3. External cardiac work (kg m $min^{-1}$)
=mean systemic arterial pressure (mmHg) $\times$ 13·6 $\times$ cardiac output (l./min) $\times 10^{-3}$

4. Peripheral vascular resistance (dynes. $s.cm^{-5}$)†
=mean systemic arterial pressure (mmHg) $\times$ 80 (i.e. per) cardiac output (l./min)

Quazodine was usually given by intravenous infusion in doses of (0·25, 0·5 or 1·0 mg/kg)/min, calculated as base, for 10 min, by means of a Sage slow injection pump. The various cardiovascular parameters were measured before each infusion and a continuous record taken during and immediately after it. Cardiac output was measured by thermodilution immediately before the infusion and once or twice during the infusion period.

In a separate series of eight experiments, the effects on arterial pressure, heart rate and aortic *dP/dt* max, of single intravenous injections of quazodine (0·5, 1·0 and 2·0 mg/kg) were compared with those of isoprenaline (0·25 $\mu$g/kg), adrenaline and noradrenaline (1·0 $\mu$g/kg) before, and after, intravenous administration of the $\beta$-adrenoceptor blocking drug alprenolol (H 56/28 ; 1·0 mg/kg).

## Results

### *General haemodynamic effects*

The general cardiovascular effects of quazodine are summarized in Table 1 and Fig. 1. There was a marked and significant ($P<0·001$) increase in left ventricular *dP/dt* max (+ve) and a reduction in LVEDP. This represents a substantial increase in myocardial contractility, particularly apparent with a dose of (0·5 mg/kg)/minute. Cardiac output was significantly ($P<0·01$) increased (from a mean of 168 $\pm$ 16 ml/kg body weight to a mean of 212 $\pm$ 25 ml/kg with a dose of (0·5 mg/kg)/min and from 172 $\pm$ 20 ml/kg body weight to 217 $\pm$ 30 ml/kg with a dose

*=418·68 J/m s° C or W/m° C ; †=$10^{-5}$ N. s. cm.

TABLE 1. *Cardiovascular effects of quazodine infusions*

| | Control | Quazodine 0·25 | Quazodine 0·5 | Quazodine (1·0 mg/kg)/min |
|---|---|---|---|---|
| Systolic blood pressure (SP) (mmHg) | 135±7 | −5±2 (12) | −7±2 (21) | −22±4 (22) |
| Diastolic blood pressure (mmHg) | 92±5 | −10±2 (12) | −14±2 (21) | −27±3 (22) |
| Heart rate (HR) (beats/min) | 196±7 | +24±4 (12) | +28±3 (21) | +35±4 (22) |
| Systolic ejection time (ms) | 124±5 | −22±5 (6) | −19±6 (11) | −20±4 (18) |
| Stroke volume (ml) | 1·88±0·25 | — | +0·15±0·08 (8) | −0·08±0·13 (6) |
| Left ventricular *dP/dt* max (+ve; mmHg $s^{-1}$) | 3629±305 | +1503±677 (4) | +1624±311 (7) | +1104±280 (7) |
| Left ventricular *dP/dt* max (−ve; mmHg $s^{-1}$) | 2564±294 | +174±263 (4) | +424±192 (7) | +414±359 (7) |
| Left ventricular end-diastolic pressure (mmHg) | 6·6±1·0 | −0·9±0·6 (5) | −4·2±1·9 (8) | −2·5±1·1 (6) |
| Cardiac effort index ($SP \times HR \times 10^{-3}$) | 277±23 | +46±9 (12) | +42±9 (21) | +17±13 (22) |
| External cardiac work (kg m $min^{-1}$) | 0·51±0·05 | — | +0·18±0·04 (8) | −0·03±0·03 (6) |

Maximum change from control during the 10 min infusion period (mean±S.E.M.). Number of observations in parenthesis.

of (1·0 mg/kg)/min). This elevation of cardiac output resulted almost entirely from the increase in heart rate. Peripheral vascular resistance was substantially reduced (Fig. 2). It is clear, both from Table 1 and from Fig. 1, that the most pronounced cardiac stimulation was obtained with a dose of (0·5 mg/kg)/minute. A larger dose ( (1·0 mg/kg)/min) resulted in pronounced systemic hypotension, par-

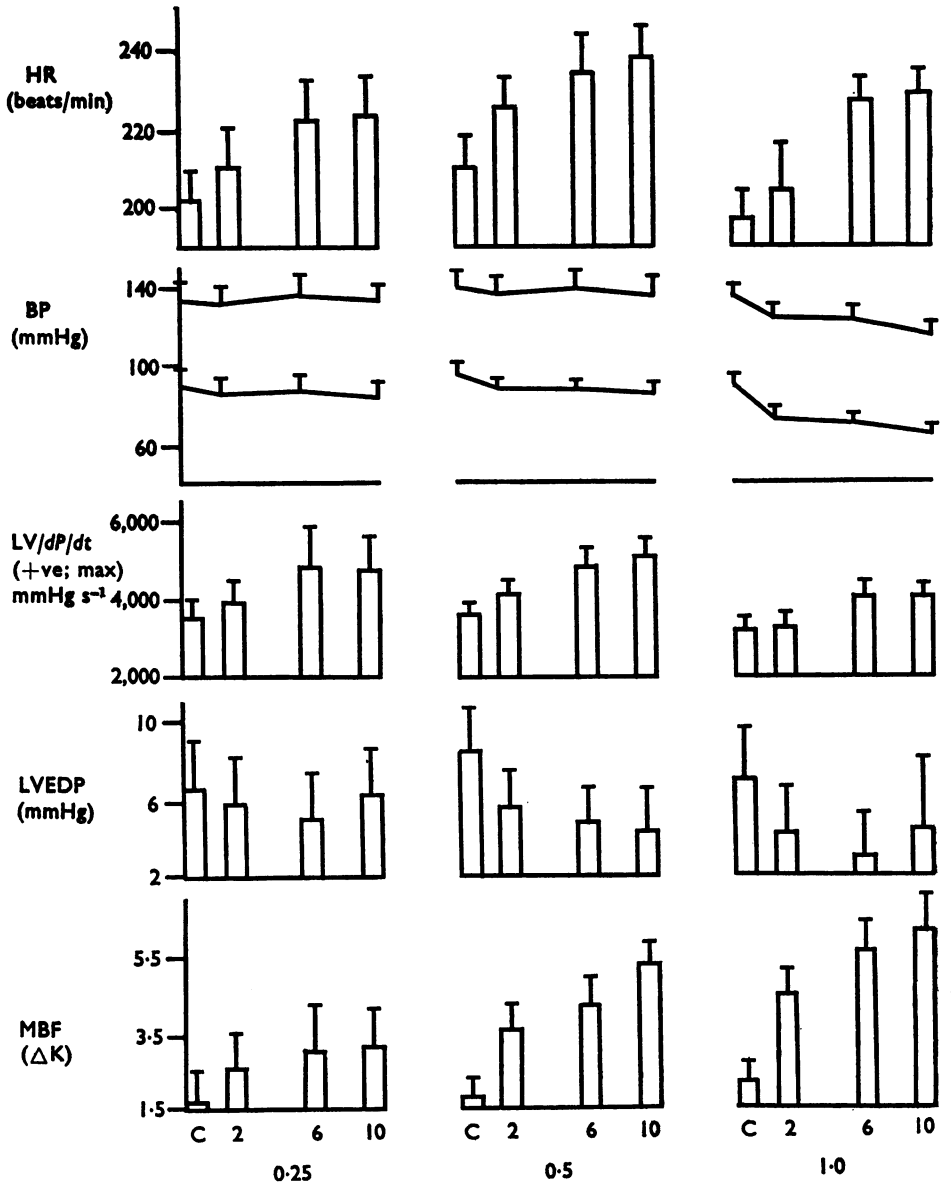



FIG. 1. Effect of infusions of quazodine ( (0·25, 0·5 and 1·0 mg/kg)/min for 10 min) on (from above) heart rate (beats/min), systolic and diastolic blood pressures (mmHg), left ventricular $dP/dt$ max (mmHg $s^{-1}$), left ventricular end-diastolic pressure (mmHg) and myocardial blood flow as myocardial thermal conductivity increment, $\Delta k$, c.g.s. units $\times 10^{-4}$). The first blocks (at the left hand side of each section, marked (c) ) represent the control (preinfusion) values (mean $\pm$ S.E. of mean) ; the other blocks represent values obtained 2, 6 and 10 min after beginning the quazodine infusion.

ticularly towards the end of the infusion period, less marked effects on left ventricular $dP/dt$ max and end-diastolic pressure, and a slight *decrease* in external cardiac work. In general, the effects of quazodine on systemic arterial pressure were most pronounced during the first 2 or 3 min of the infusion; thereafter, pressure tended to recover, falling again towards the end of the 10 min infusion period when the larger dose was used. The maximum effects on left ventricular pressure, $dP/dt$ max and heart rate were, however, usually obtained towards the end of the infusion period (Fig. 1). Recovery of these parameters was obtained within 20–30 min of terminating the infusion (see Fig. 3).

*Effects of quazodine on myocardial and liver blood flow*

Infusions of quazodine (twenty-five in all) always very markedly increased local blood flow around the implanted myocardial recorder (Fig. 4). The mean thermal conductivity increment ($\Delta k$) in the apical region of the cat myocardium was $2{\cdot}19 \pm 0{\cdot}51 \times 10^{-4}$ cal/cm s° C, which is much smaller than that obtained in the anterior wall of the myocardium in the region supplied by the anterior ventricular branch of the left descending coronary artery. Increases between 70 and 540% were obtained after quazodine and, as the coronary perfusion pressure was reduced, this indicates a very considerable decrease in the flow resistance of the vessels of the myocardial microcirculation ($53 \pm 15\%$ with a dose of 0·25 (mg/kg)/min; $68 \pm 7\%$ with a dose of (0·5 mg/kg)/min and $76 \pm 5\%$ with (1·0 mg/kg)/min). These changes in flow and resistance were maintained throughout the infusion period (Fig. 1) and for up to 30 min after the infusion was terminated. The times taken for flow to return to preinfusion levels were $16 \pm 4$ min, $27 \pm 4$ min and $23 \pm 3$ min for doses of (0·25, 0·5 and 1·0 mg/kg)/min, respectively.

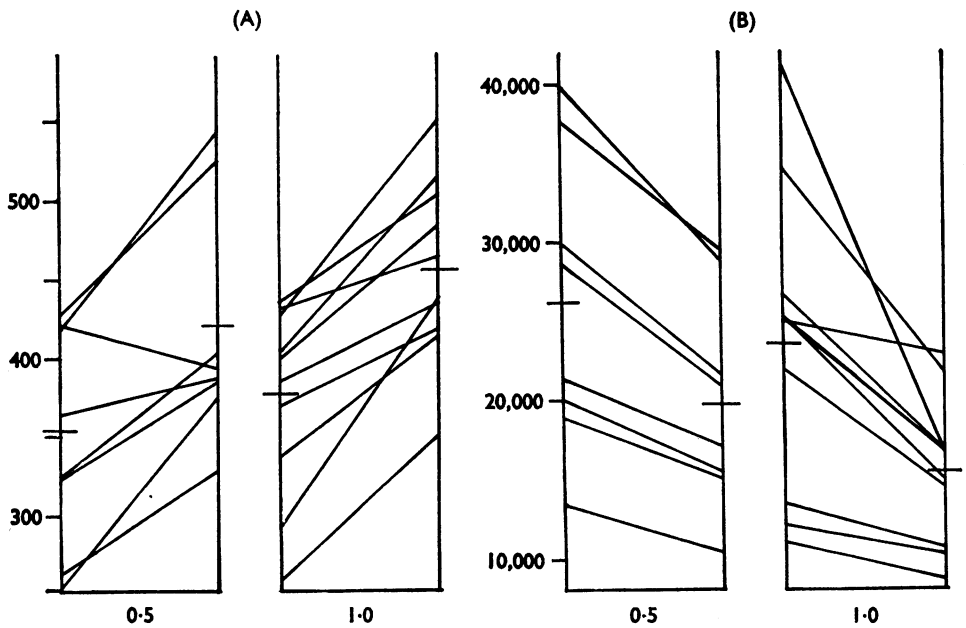



FIG. 2. Effect of quazodine ((0·5 and 1·0 mg/kg)/min) on cardiac output (ml/min) (A) and on peripheral vascular resistance ((dynes/s)/cm$^{-5}$) (B). The means of each group are represented by the short horizontal bars.

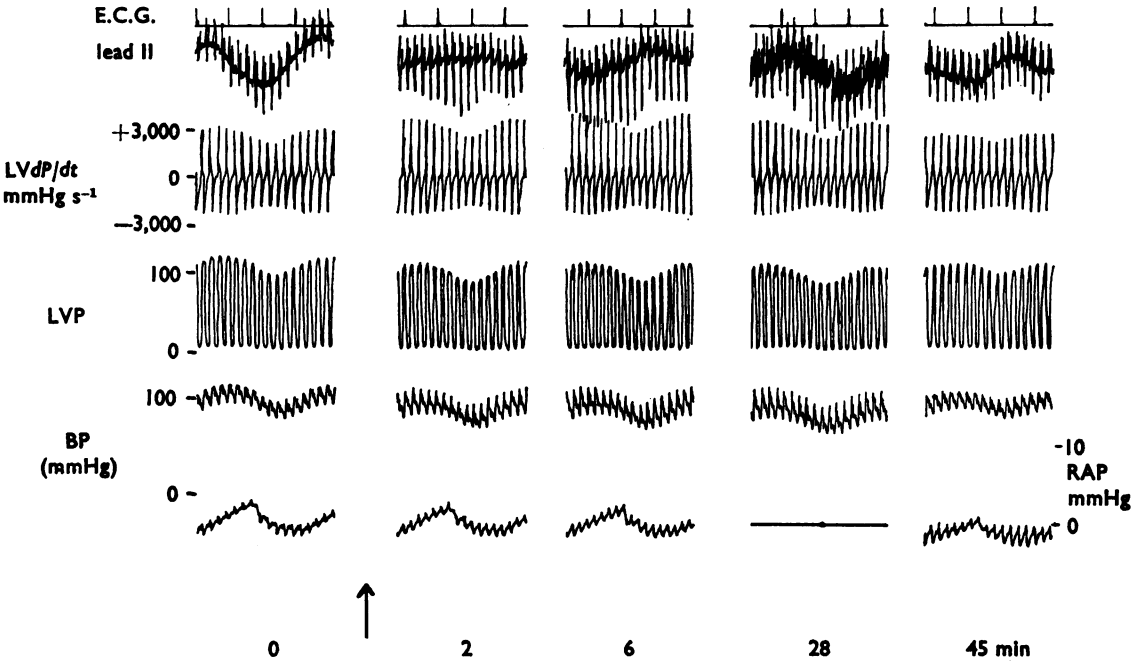



FIG. 3. The effects of a 10 min infusion of quazodine ((0·5 mg/kg)/min at the arrow; time 0 min) on the electrocardiogram (lead II), left ventricular $dP/dt$ max (mmHg $s^{-1}$), left ventricular pressure (mmHg), femoral arterial pressure (mmHg) and right atrial pressure (mmHg). Notice that the effect of quazodine on left ventricular $dP/dt$ max was still apparent 18 min after the infusion was terminated. Time scale 1 second.

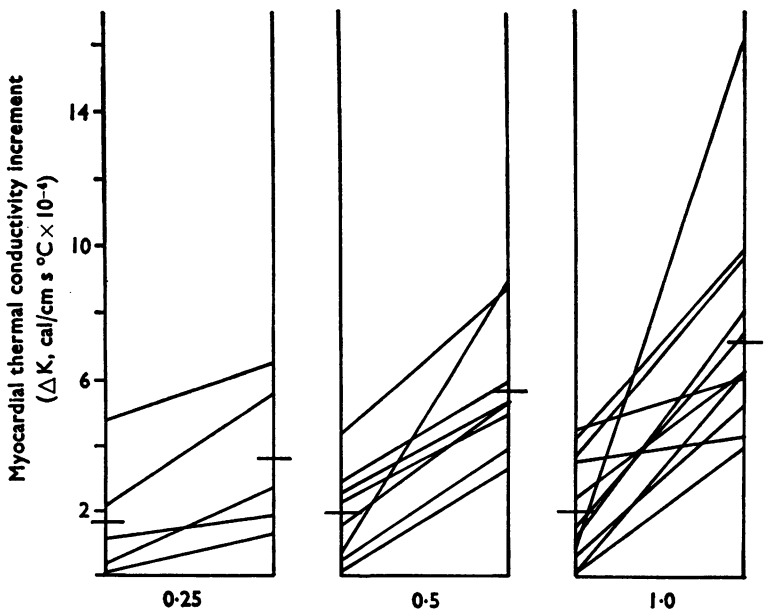



FIG. 4. Effect of quazodine infusions ((0·25, 0·5 and 1·0 mg/kg)/min) on myocardial blood flow (as myocardial thermal conductivity increment, Δk, c.g.s. units $\times 10^{-4}$). The means of each group are represented by the short horizontal bars.

Changes in liver blood flow were, in contrast, undramatic. The mean resting liver thermal conductivity increment in these experiments was $1{\cdot}52 \pm 0{\cdot}59 \times 10^{-4}$ cal/cm s° C; a dose of (0·25 mg/kg)/min of quazodine decreased liver blood flow (change in $\Delta k = 0{\cdot}33 \times 10^{-4}$ cal/cm s° C), presumably because of the slight systemic hypotension. A dose of (0·5 mg/kg)/min slightly increased liver blood flow (increase in $\Delta k$, $0{\cdot}2 \times 10^{-4}$ cal/cm s° C). There was a more substantial increase in flow with a dose of (1·0 mg/kg)/min (increase in $\Delta k$, $0{\cdot}5 \times 10^{-4}$ cal/cm s° C). It can be concluded that quazodine has relatively little effect on liver blood flow in doses which substantially increase flow in the myocardium.

### *Effects on myocardial metabolic heat production*

These are summarized in Table 2. In seventeen experiments in which metabolic heat production was assessed, quazodine ( (0·25, 0·5 and 1·0 mg/kg)/min) increased 'corrected temperature' in six experiments, decreased 'corrected temperature' in eight and had no effect (that is <0·03° C) in the remaining three. These changes are much less marked than those which result from catecholamine administration in cats, where the mean change is of the order of +0·06° C (for adrenaline and isoprenaline) and +0·04° C (for noradrenaline; Parratt & Wadsworth, 1970). Our conclusion is that quazodine has little consistent effect on myocardial metabolic heat production in doses which markedly increase cardiac output, left ventricular $dP/dt$ max and the cardiac effort index (Table 1).

### *Effects of quazodine after β-adrenoceptor blockade*

A comparison of the effects of single injections of quazodine (0·5, 1·0 and 2·0 mg/kg) with those of isoprenaline (0·25 μg/kg), adrenaline and noradrenaline (1·0 μg/kg) on systemic blood pressure, heart rate and descending aortic $dP/dt$ is shown in Fig. 5. The effects of quazodine on diastolic and systolic pressures, heart rate, descending aortic $dP/dt$ and also on myocardial blood flow, were largely unaltered by a dose of alprenolol (1·0 mg/kg) which abolished the isoprenaline induced changes in aortic $dP/dt$ and diastolic blood pressure, and which markedly reduced isoprenaline induced tachycardia. This dose of alprenolol also abolished tachycardia produced by adrenaline, reversed its action on diastolic blood pressure and potentiated its effect on systolic blood pressure (Fig. 5).

TABLE 2. *Changes in myocardial metabolic heat production (as 'corrected temperature', °C) induced by intravenous infusions of quazodine*

| | Quazodine (mg/kg)/min | | |
|---|---|---|---|
| | 0·25 | 0·5 | 1·0 |
| | +0·12 | +0·05 | +0·02 |
| | +0·10 | +0·04 | −0·02 |
| | +0·06 | +0·04 | −0·05 |
| | −0·08 | −0·01 | −0·05 |
| | | −0·06 | −0·07 |
| | | −0·08 | −0·07 |
| | | | −0·32 |
| Mean | +0·05° C | −0·003° C | −0·07° C |

## Discussion

These experiments confirm and extend the findings of Aviado *et al.* (1967) and of Carr *et al.* (1967) in canine heart-lung and right heart bypass preparations, that quazodine is an active cardiac stimulant with coronary vasodilator properties. Our

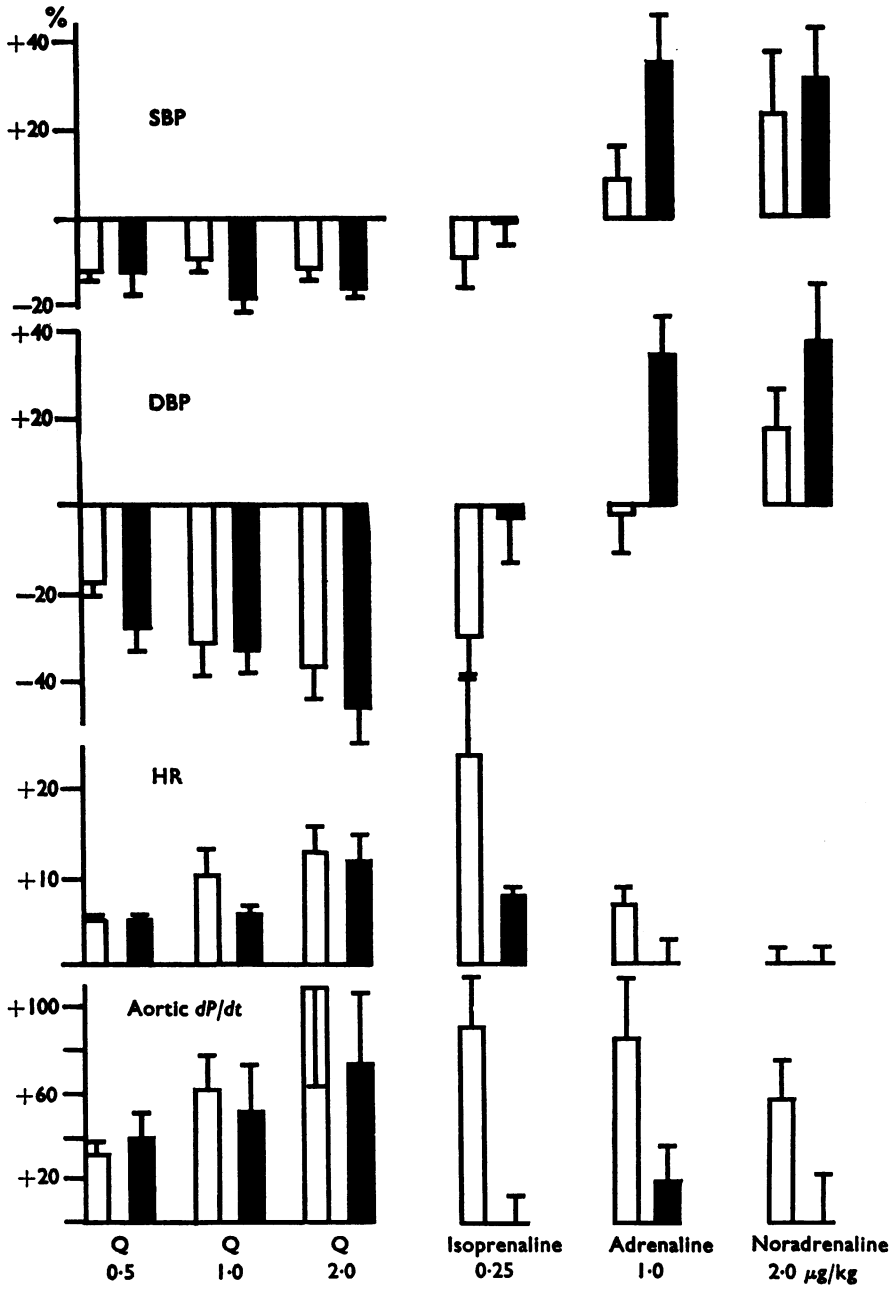



FIG. 5. Blood pressure, heart rate and aortic $dP/dt$ responses to intravenous injections of quazodine (0·5, 1·0 and 2·0 mg/kg), isoprenaline (0·25 μg/kg), adrenaline (1·0 μg/kg) and noradrenaline (1·0 μg/kg) before (open blocks) and after (filled in blocks) the β-adrenoceptor blocking drug alprenolol (10 mg/kg). Values are mean % changes from control ± S.E. of mean.

experiments in closed-chest cats (at times spontaneously breathing) demonstrate that quazodine markedly increases cardiac output, external cardiac work and also left ventricular $dP/dt$ max, despite a reduction in left ventricular end-diastolic pressure (LVEDP). Taken together, this is evidence for an increase in myocardial contractility. These effects lasted throughout the 10 min infusion period and for up to 30 min afterwards. The maximum effects on contractility occurred with a dose of (0·5 mg/kg)/min (that is, 5 mg/kg total); double this dose did not further increase these parameters of contractility and, in fact, had less effect on left ventricular $dP/dt$ max. This larger dose also had a more pronounced hypotensive effect and actually decreased external cardiac work. Previous authors (Aviado *et al.*, 1967) have demonstrated a degree of cardiac depression with very large doses of quazodine and also noticed the occurrence of (unspecified) cardiac arrhythmias (Aviado *et al.*, 1967; Carr *et al.*, 1967). Only very occasional arrhythmias (mainly nodal) were noticed in our experiments with a total dose of 10 mg/kg.

In contrast to the effect of catecholamines, the cardiac stimulant effect of quazodine appears to be uninfluenced by a reduction in blood pH. Thus Aviado (1965) describes one experiment, in a dog in shock from extensive intrathoracic manipulation, in which the cardiac stimulant effect of intracoronary quazodine was still apparent during carbon dioxide inhalation. In cats subjected to endotoxin shock, which results in a severe metabolic acidosis, myocardial depression and systemic hypotension, we have demonstrated that quazodine is capable of markedly increasing myocardial contractile force at times when the haemodynamic effects of adrenaline and noradrenaline are much reduced or abolished (Parratt & Winslow, unpublished observations).

Local blood flow in the myocardium was very substantially increased by the drug and some of these flow increases were greater than any previously seen in this laboratory with coronary vasodilator drugs. Some of this increase in local (nutritive) flow is no doubt secondary to the increase in contractility, but a large proportion must be due to a direct vasodilator action of the drug on the vessels of the microcirculation. Perfusion pressure was usually reduced and thus myocardial vascular resistance to flow was very markedly decreased. Since diastolic blood pressure and total peripheral vascular resistance were also reduced it is clear that vasodilatation occurs in other areas of the body apart from the myocardium. The most likely sites would seem to be skeletal muscle and skin as the simple measurement of muscle, skin and arterial temperatures during quazodine infusions demonstrate. It is of interest, however, that liver blood flow (as assessed by thermal conductivity measurements) was not substantially increased except with the larger dose; it would be of further interest to analyse the effect of the drug on intestinal blood flow.

The effects on myocardial metabolic heat production were of particular interest, in view of the findings of Carr *et al.* (1967) that quazodine increases myocardial contractility without increasing myocardial oxygen consumption. Drugs (like the catecholamines) which increase contractility, invariably increase the production of heat by cardiac muscle. This is partly dependent upon changes in tension and is partly independent of tension (and muscle length) (Gibbs, 1967). Thus, using 'corrected temperature' as a qualitative index of myocardial heat production *in vivo*, it has been shown that catecholamines increase total heat production and that this is abolished (or even reversed) by $\beta$-adrenoceptor blockade (Parratt 1969; Parratt &

Wadsworth, 1970). These changes in heat production and contractility are, of course, associated with marked increases in myocardial oxygen consumption. In contrast, the effects of quazodine on myocardial metabolic heat production, despite the marked changes in contractility, were unspectacular (Table 2). It is also possible that where increases did occur, the reflex liberation of catecholamines from sympathetic nerves and from the adrenal medulla, as a result of systemic hypotension, may have been partly responsible.

An explanation of this phenomenon may be found in variations in two of the major components contributing to cardiac oxygen consumption ($M\dot{V}O_2$) and heat production. These are the contractile state of the heart (which is reflected in the rate of pressure development and the systolic ejection rate) and the tension in the wall of the ventricle (which is a direct function of intraventricular pressure and radius; Sonnenblick, Ross & Braunwald, 1968). Thus, cardiac glycosides increase $M\dot{V}O_2$ in the normal heart but may decrease it when the ventricle is enlarged (as in cardiac failure) by reason of the concomitant reduction which takes place in wall tension. A degree of cardiac enlargement would almost certainly be present in the right heart bypass experiments of Carr *et al.* (1967) and perhaps also in our own studies in cats anaesthetized with pentobarbitone and subjected to thoracotomy. Thus a marked decrease in LVEDP occurred in both groups of experiments after the administration of quazodine. It could be, therefore, that the failure of quazodine to increase $M\dot{V}O_2$, or to consistently increase metabolic heat production, results from a reduction in intramyocardial wall tension. The situation is thus analogous to the effect of digitalis on the overtly failing heart.

This work was supported by the Medical Research Council and by a grant for apparatus from the Wellcome Trust. E. W. is a Medical Research Council scholar. We wish to thank Miss Linda McInnes and Miss Maureen Divers for skilled assistance and Drs. Paul Lish and Gordon McKinney (Mead Johnson Research Centre, Evansville, Indiana) for generous supplies of quazodine.

## REFERENCES

AVIADO, D. M. (1965). Pharmacologic approach to the treatment of shock. *Ann. intern. Med.*, **62**, 1050–1059.

AVIADO, D. M., FOLLE, L. E. & PISANTY, J. (1967). The cardiopulmonary effects of a quinazoline (MJ 1988); cardiac stimulant, pulmonary vasodilator and bronchodilator. *J. Pharmac. exp. Ther.*, **155**, 76–83.

CARR, P. W., COOPER, T., DAGGETT, W. M., LISH, P. M., NUGENT, G. G. & POWERS, P. C. (1967). Effects of compound MJ-1988 on myocardial contractility, oxygen consumption, coronary blood flow and vascular resistance. *Br. J. Pharmac. Chemother.*, **31**, 56–65.

GIBBS, C. L. (1967). Changes in cardiac heat production with agents that alter contractility. *Aust. J. exp. Biol. med. Sci.*, **45**, 379–392.

GRAYSON, J. & MENDEL, D. (1961). Myocardial blood flow in the rabbit. *Am. J. Physiol.*, **200**, 698–974.

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.

HOSIE, J. F. (1962). Thermal-dilution technics. *Circulation Res.*, **10**, 491–504.

LISH, P. M., COX, R. M., DUNGAN, K. W. & ROBBINS, S. I. (1964). Some nonadrenergic bronchodilator and cardiac stimulating agents. *Pharmacologist*, **6**, 181.

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.

PARRATT, J. R. (1969). The effects 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. & WADSWORTH, R. M. (1969). Myocardial and haemodynamic effects of the beta-adrenoceptor blocking drug alprenolol (H56/28) in anaesthetized cats. *Br. J. Pharmac.*, **37**, 357–366.

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 (H56/28) in anaesthetized 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.

SONNENBLICK, E. H., ROSS, J. & BRAUNWALD, E. (1968). Oxygen consumption of the heart. Newer concepts of its multifactoral determination. *Am. J. Cardiol.*, **22**, 328–336.

WILLIAMS, J. C. P., O'DONOVAN, T. P. B. & WOOD, E. H. (1966). A method for the calculation of areas under indicator-dilution curves. *J. appl. Physiol.*, **21**, 695–699.

(*Received December* 14, 1970)