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Haemodynamic and coronary effects of quazodine in cats with developing myocardial infarcts

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Acute ligation of the descending branch of the left coronary artery in anaesthetized cats resulted, within 1–2 h, in a 30% decrease in local blood flow in the region mainly supplied by the ligated vessel, a fall in systemic blood pressure, in cardiac output, and in left ventricular dP/dt max (LVdP/dt). There was electrocardiographic evidence of myocardial ischaemia (pronounced ST elevation). In these animals with developing myocardial infarcts, intravenous infusions of quazodine (MJ1988; 6,7-dimethoxy-4-ethyl-quinazoline) markedly increased myocardial contractility and local myocardial blood flow in the developing infarct, and decreased systemic arterial pressure, peripheral vascular resistance and left ventricular end-diastolic pressure, effects similar to those observed in normal cats. The increase in cardiac contractility (cardiac output and LVdP/dt) occurred without a concomitant increase in myocardial metabolic heat production. This 'oxygen sparing effect' probably results from a decrease in left ventricular wall tension. It is suggested that quazodine warrants further investigation as a cardiac stimulant in power failure following myocardial infarction in man.

Quazodine (MJ 1988; 6,7,-dimethoxy-4-ethyl-quinazoline has been shown to possess cardiac stimulant and vasodilator actions and to increase blood flow through the myocardium (Lish, Cox & others, 1964; Aviado, Folle & Pisanty, 1967; Parratt & Winslow, 1971a). Myocardial stimulation induced by the drug can occur without significant increases in myocardial oxygen consumption (Carr, Cooper & others, 1967) or in myocardial metabolic heat production (Parratt & Winslow, 1971a). The effects of quazodine on myocardial contractility (Carr & others, 1967, Parratt & Winslow, 1971a) and on vascular and extravascular smooth muscle (Parratt & Winslow, 1971b) are uninfluenced by β-adrenoceptor blockade and evidence from broken cell preparations (Amer & Browder, 1971) and from smooth muscle experiments (Parratt & Winslow, 1971b) suggests that its effects are mediated, at least partly, through inhibition of phosphodiesterase.

In view of the combination of increased myocardial contractility, improved tissue perfusion and the apparent 'oxygen sparing' effect of quazodine, it was of interest to examine the effects of the drug in experimental myocardial infarction, where cardiac function is impaired as a result of reduced nutritional blood flow. This impairment of functional myocardial contractility results in a decline in stroke volume (Ross, 1967; Wilson, Chiscano & Quadros, 1967; Kuhn, 1970) with a resultant decrease in systemic arterial pressure and consequently in coronary perfusion. Left ventricular end-diastolic pressure (LVEDP) is frequently elevated (Cohn & Tristani, 1967) and this would reduce the effective driving pressure responsible for the perfusion of the sub-endocardial plexus (Estes, Entman & others, 1966). Such an elevation of end-

diastolic pressure would ultimately lead to further muscle damage, especially of endocardial regions. The fact that quazodine decreases LVEDP in anaesthetized animals, increases myocardial contractility and dilates both myocardial and pulmonary vessels prompted us to examine the general haemodynamic effects of this substance in conditions simulating the early stages of myocardial infarction, in particular, its effects on myocardial blood flow in the ischaemic area.

METHODS

Thirteen cats of either sex and weighing between 2 and 3·9 kg were anaesthetized with sodium pentobarbitone (30 mg/kg) given intraperitoneally. The animals were ventilated with room air using a Palmer pump and the respiratory stroke volume adjusted such that after thoracotomy the arterial pO_2 was between 80 and 100 mg Hg (1 mm Hg = 1·333 mbar). Rectal and mid-oesophogeal temperatures were measured using direct recording thermocouples (Ellab, Copenhagen) and were maintained between 36·5 and 38°. Left ventricular systolic and end-diastolic pressures (LVSP; LVEDP), left ventricular dP/dt max, heart rate, arterial pressure, right atrial pressure and the electrocardiogram (lead I or II) were recorded as previously described (McInnes & Parratt, 1969; Parratt & Wadsworth, 1969) on an eight channel Elema Schönander recorder (Mingograph 81).

Cardiac output was measured using a thermal dilution technique (Hosie, 1962). A 36 s.w.g. copper-constantan junction was inserted via 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 and Zonen BD5 Recorder (50 μV for a full scale of 20 cm = 1·2°). The paper speed was 200 mm/min. A bolus of 2 ml of saline at room temperature (18–25°) 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). The recorder was implanted in the anterior wall of the left ventricle such that ligation of a major branch of the left descending coronary artery would compromise local blood flow in the area around the recorder. The output from the heated thermocouple was fed directly into a second Kipp and Zonen BD5 recorder (100 μV full scale of 20 cm $\equiv$ 2·5°). The cold (reference) junction was positioned in the aortic arch via the left common carotid artery. Full experimental details and the methods of calculating 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 previously (Grayson & Parratt, 1966; McInnes & Parratt, 1969; Parratt, 1969). The following data were derived:

1. Myocardial vascular resistance (arbitrary units) = diastolic arterial blood pressure (mm Hg)/myocardial thermal conductivity increment (Δk; as cal/cm s°C $\times$ 10^{-4})*. It should be noted that after coronary artery ligation the perfusion pressure below the level of the ligature is not equal to the diastolic pressure and therefore only directional changes in MVR can be assessed. The figures quoted in the text can only be taken to represent a qualitative increase or decrease in MVR.
2. Cardiac effort index (Robinson, 1967) = systolic blood pressure (mm Hg) $\times$ heart rate (beats/min) $\times$ 10^{-3}.

* = 418·68 J/m s°C.

3. Peripheral vascular resistance (dynes s cm^{-2}) = mean systemic arterial pressure (mm Hg) × 80/cardiac output (litres/min).
4. Stroke volume = cardiac output (ml/min)/heart rate (beats/min).

Infusions of quazodine (0·5 mg/kg/min base) were given, for a 10 min period, before, and up to 4 h after, coronary artery ligation. The various cardiovascular parameters were measured before each infusion and a continuous record taken during, and for up to 15 min after, the termination of the infusion. Cardiac output was measured immediately before the infusion commenced and just before the infusion was terminated.

RESULTS

Haemodynamic and coronary effects of quazodine in cats with developing myocardial infarcts

The direct effects of coronary artery ligation are summarized in Table 1 and in Figs 1 and 2. After ligation, heart rate increased whilst blood pressure, cardiac

Table 1. *Direct effects of coronary artery ligation in cats. Results are means of eight to eleven experiments* ± s.e.

		Hours after ligation		
	Pre-ligation	1	2	3
Systolic blood pressure (mm Hg) ..	147 ± 8	129 ± 9	149 ± 8	111 ± 13*
Diastolic blood pressure (mm Hg) ..	103 ± 6	83 ± 7*	87 ± 4*	70 ± 10*
Mean blood pressure (mm Hg) ..	118 ± 7	98 ± 7	108 ± 4	83 ± 12*
Heart rate (beats/min)	200 ± 7	202 ± 9	239 ± 16*	203 ± 10
Cardiac effort index	29·5 ± 2·0	26·3 ± 2·1	35·3 ± 4·4	22·0 ± 2·2
LVEDP (mm Hg)	5·6 ± 1·5	6·4 ± 0·7	4·1 ± 0·8	
LVdP/dt max (mm Hg s^{-1})	3570 ± 358	2679 ± 109*	3604 ± 389	
Cardiac output ml/kg per min) ..	136·3 ± 9·1	107·3 ± 17·5	93·3 ± 13·5*	
Stroke volume (ml/beat)	2·0 ± 0·2	1·5 ± 0·2	1·4 ± 0·2*	
Myocardial blood flow (Δk; cal/cm s°C × 10^{-4})	4·8 ± 1·05	3·11 ± 0·63*	3·65 ± 1·12	3·65 ± 0·82

*P < 0·05

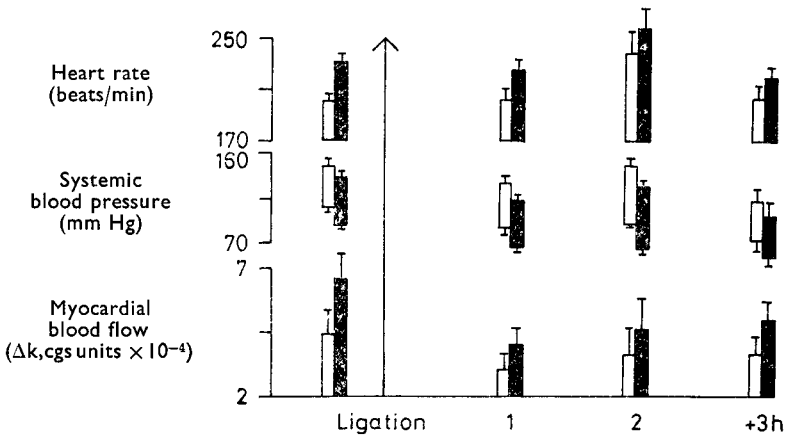

FIG. 1. The effect of quazodine (0·5 mg/kg per min, i.v.) on heart rate (beats/min), systemic arterial systolic and diastolic blood pressures (mm Hg) and on myocardial blood flow (as myocardial thermal conductivity increment, Δk, c.g.s. units × 10^{-4}) before and after acute coronary artery ligation. The open columns represent pre-quazodine levels (mean ± s.e.); the closed columns values during the quazodine infusion.

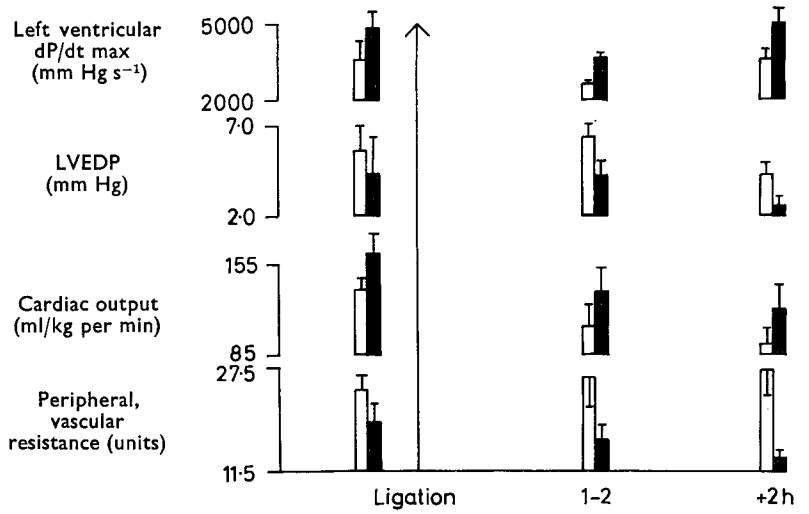

FIG. 2. The effect of quazodine (0·5 mg/kg per min) on left ventricular dP/dt max (mm Hg s^{-1}), left ventricular end-diastolic pressure (mm Hg), cardiac output (ml/kg per min) and peripheral vascular resistance, before and after acute coronary artery ligation. The open columns represent pre-quazodine levels (mean ± s.e.); the closed columns values during the infusion.

output, stroke volume, LVdP/dt, the cardiac effort index and myocardial blood flow decreased. There was a slight decrease (0·4 mm Hg) in right atrial pressure 3 to 4 h after ligation. Peripheral vascular resistance was generally slightly increased (by 8–12%). Heart rate and myocardial blood flow showed a tendency to re-attain pre-ligation levels 2 to 4 h after ligation and LVdP/dt max was slightly elevated 2 to 3 h after ligation. LVEDP was increased 1 to 2 h after ligation but between 2 and 3 h it fell below pre-ligation values. The electrocardiographic record showed marked ST elevation, indicative of myocardial ischaemia, which commenced immediately after ligation and was present throughout the remainder of the experiment. Typical records, taken before and 2 h after ligation, are illustrated in Fig. 3.

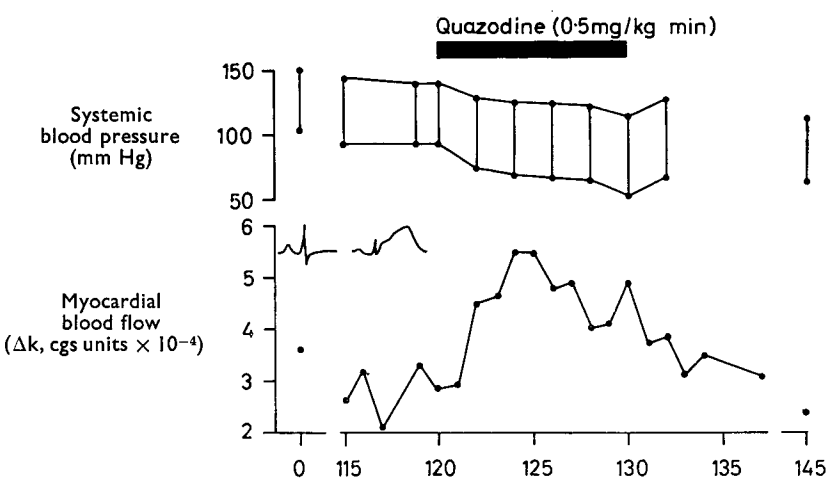

FIG. 3. The effect of quazodine (0·5 mg/kg per min, represented by the solid horizontal bar) on systemic blood pressure (mm Hg) and myocardial blood flow 2 h after coronary artery ligation. Pre-ligation control values are given on the left. Ligation decreased local myocardial blood flow and elevated the ST segment of the electrocardiogram (lead II).

Table 2 and Figs 1 and 2 summarize the maximum effects of quazodine on various cardiovascular parameters before and for periods of up to 4 h after coronary artery ligation. Quazodine increased heart rate, although these increases became progressively less marked as the time from ligation increased. The quazodine-induced increases in LVdP/dt max before and after ligation were comparable. These increases were consistently accompanied by a fall in LVEDP. These two effects taken together represent a substantial increase in myocardial contractility in response to the drug. It also increased the cardiac output to the same extent both before and after ligation and since quazodine-induced tachycardia was less marked after ligation, this indicates a greater effect on stroke volume. In fact stroke volume was unaffected by quazodine before ligation but was slightly increased (by about 10%) after ligation. The cardiac

Table 2. *Haemodynamic changes (from absolute values shown in Table 1) induced by quazodine in cats before and after coronary artery ligation.* Results are the means of eight to eleven experiments ± s.e. * denotes significant differences from the pre-ligation effect of quazodine. ($P < 0.05$).

		Hours after ligation		
	Pre-ligation*	1	2	3
Systolic blood pressure (mm Hg)	−14±3	−19±3	−24±3	−16±5
Diastolic blood pressure (mm Hg)	−18±3	−19±3	−25±4	−16±3
Mean blood pressure (mm Hg)	−16±3	−20±3	−25±3*	−15±3
Heart rate (beats/min)	+34±4	+23±4	+19±5	+16±14
Cardiac effort index	+2·6±1·6	−1·6±1·1	−3·9±1·3*	−0·33±2·2
Left ventricular systolic pressure (mm Hg)	+9±7	−14±8·6	0±8	
LVEDP (mm Hg)	−1·4±1·6	−2·3±0·8	−1·8±0·4	
LVdP/dt max (mm Hg s^{-1})	+1281±346	+1016±173	+1400±505	
Cardiac output (ml/kg per min)	+33±9·3	+26·5±4·4	+27·4±6·8	
Stroke volume (ml/beat)	−0·06±0·17	+0·15±0·07	+0·15±0·09	
Peripheral vascular resistance (dynes s cm × 10^{-2})	−5·4±2·7 (−22%)	−9·7±1·9* (−37%)	−13·7±6·3* (−50%)	
Myocardial blood flow Δk; cal/cm s°C × 10^{-4})	+2·15±0·43 (+48%)	+0·95±0·25* (+24%)	+0·96±0·34* (+26%)	+1·37±0·55 (+3 8%)

* Absolute control values shown in Table 1. All changes in this Table are significantly different ($P < 0.001$) from control saline infusions.

effort index showed a slight increase in response to quazodine before ligation and slight decreases after ligation, the most marked reductions being apparent 2 h after ligation when the resting cardiac effort index had risen to values considerably above the pre-ligation levels. Both before and after ligation quazodine was without effect on right atrial pressure. The fall in blood pressure it induced became more marked up to 2 h after ligation but at 3 h was comparable to that observed before ligation despite the existing hypotension. Similarly, the quazodine-induced decrease in peripheral vascular resistance became progressively more marked as the time from ligation increased. Left ventricular pressure was slightly increased by quazodine before ligation, substantially decreased by it 1 to 2 h after ligation and unaffected by it 2 to 3 h after ligation.

The effects of the drug on the electrocardiogram appeared to depend on the degree of induced tachycardia. In animals where a moderate increase in heart rate was observed (up to 14 beats/min) the degree of ST elevation was reduced. Where the heart rate was increased by 24–36 beats/min, the ecg was unchanged. Further quazodine-induced increases in heart rate (up to 54 beats/min) resulted in a more ischaemic myocardium.

Effects of quazodine on myocardial blood flow and metabolic heat production

Before coronary artery ligation, quazodine increased local blood flow around the recorder by 48%. The quazodine-induced increases in myocardial blood flow were much less up to 2 h after ligation, an increase of only 24% being observed at this time. However 3 h after ligation, when the resting blood flow was tending toward pre-ligation values, the drug produced an increase in local blood flow of 38%. This increase in myocardial blood flow, together with the decrease in diastolic blood pressure induced by quazodine, represents a substantial reduction in myocardial vascular resistance. This reduction in vascular resistance in the ischaemic myocardium in response to the drug was estimated to be about 50% assuming that the perfusion pressure in the infarcted area was of about 25 mm Hg. Fig. 3 shows typical effects of an infusion of quazodine on blood pressure and on myocardial blood flow 2 h after ligation. It can be seen that the fall in blood pressure and the increase in myocardial blood flow induced by the drug are maintained throughout the period of the infusion. In five experiments, myocardial 'excess temperature' was calculated. Before ligation quazodine increased heat production in four animals and was without effect in the remaining one. The mean increase in excess temperature was 0·08°. Out of a total of 12 observations, made after ligation, quazodine increased excess temperature in 6, decreased it in 2 and had no effect in 4 ($<0·03°$). The mean changes induced by quazodine 1, 2 and 3 or more h after ligation were $+0·05$, $-0·03$ and $+0·07°$ respectively.

DISCUSSION

The results indicate that the cardiovascular changes induced by quazodine in cats with developing myocardial infarcts and in the early stages of shock are qualitatively similar to those seen in the normal animal. Quantitative differences are however apparent. Although the positive inotropic effects of quazodine, as evidenced by increased LVdP/dt max and cardiac output, remain unchanged after ligation, quazodine had less marked chronotropic effects and more marked vasodilator effects. In these experiments there is evidence of increased sympathetic discharge after coronary artery ligation. Heart rate increased, peripheral vascular resistance also showed a slight increase and the immediate post-ligation fall in LVdP/dt max was seen to recover 2 to 3 h after ligation. In some cases it exceeded pre-ligation values. Two h after ligation a partial recovery in blood pressure was evident and the cardiac effort index had risen above pre-ligation values. The results of previous experiments (Parratt & Winslow, 1971a) suggested that quazodine releases catecholamines from the adrenal medulla and under normal circumstances blood pressure tended to rise toward control values during the latter part of an infusion of the drug. This latter effect is probably the result of vasoconstriction induced by released catecholamines. It may be therefore that in the presence of an already over active sympathetic discharge, this compensation for the vasodilator effects of quazodine is less marked and

blood pressure and peripheral vascular resistance are allowed to fall to much lower levels in response to continued infusion.

The less marked effect of quazodine on heart rate after ligation does not seem to be due to the existing tachycardia. Three h after ligation the heart rate was much less than that observed at 2 h. However, quazodine produced a smaller increase in heart rate at this time. This reduced chronotropic effect of the drug after ligation would appear to be beneficial since there was electrocardiographic evidence of a less ischaemic myocardium during the infusion provided the heart rate was not markedly increased.

The quazodine-induced increases in coronary blood flow were less marked after coronary ligation. Nevertheless, 3 h after ligation the mean percentage increase in myocardial (infarct) blood flow was 38% (compared to a pre-ligation increase of 44%). This increased flow is due to reduced vascular resistance since coronary perfusion pressure was decreased. The fall in LVEDP induced by quazodine might also contribute to increased myocardial blood flow. By reducing coronary extravascular support which, in the case of a raised LVEDP, might be sufficient to compress or even occlude collateral vessels in the endocardial regions, myocardial perfusion in these inner layers would be improved. Although the increases in LVEDP seen in these experiments following coronary ligation were probably not of sufficient magnitude to grossly impede flow in these areas, this property of quazodine is worth consideration in regard to those cases of human myocardial infarction where LVEDP is markedly elevated.

Probably the most important result of this study relates to the effects of quazodine on myocardial metabolic heat production. In only half the observations made did quazodine produce an increase after ligation; 2 h after ligation, when cardiac contractility was markedly depressed, quazodine produced a decrease in metabolic heat production whilst increasing contractility. At this time therefore, quazodine was improving cardiac performance whilst proportionately decreasing the energy requirements of the heart. Since blood flow through the myocardium was only increased by 24% at this time, it would appear that this 'oxygen sparing' effect of quazodine is not due to increased flow through the ischaemic region of the myocardium. It seems more likely to be due to the reduction in LVEDP. This would decrease intramural wall tension and hence that large proportion of total myocardial oxygen consumption due to resting tension (Sonnenblick, Ross & Braunwald, 1968).

In view of the cardiovascular effects of quazodine in cats with developing myocardial infarcts, notably its positive inotropic, coronary vasodilator and 'oxygen sparing' effects, it is suggested that this compound warrants study in the treatment of human myocardial infarction.

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