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Myocardial and haemodynamic effects of phentolamine

P. K. DAS AND J. R. PARRATT

Department of Pharmacology, University of Strathclyde, Glasgow, C1

Summary

1. In cats anaesthetized with pentobarbitone, intravenous infusions of phentolamine ((10–50 μg/kg)/min for 5 min) increased heart rate, left ventricular dp/dt max (without increasing end-diastolic pressure), aortic dp/dt, cardiac output, myocardial blood flow and metabolic heat production.

2. Phentolamine-induced increases in myocardial contractility occurred irrespective of the direction or magnitude of the blood pressure change and were maintained well beyond the actual infusion period.

3. In cats treated with alprenolol, bretylium or reserpine there was no evidence of increased cardiac contractility following phentolamine administration.

4. It is concluded that phentolamine, in doses less than those required to produce significant α-adrenoceptor blockade, increased myocardial contractility through an effect on the sympathetic nervous system.

Introduction

There is a considerable difference of opinion concerning the value of α-adrenoceptor blocking agents in clinical shock. Phenoxybenzamine increases the survival time of animals subjected to haemorrhagic, traumatic and endotoxin shock (Bloch, Pierce, Manax & Lillehei, 1965) and the results of some studies suggest that this drug, and also phentolamine, might be of value in clinical shock (Nickerson, 1963 ; Bradley & Weil, 1965 ; Freeman, 1969). The present pharmacological basis for the therapeutic use of α-adrenoceptor blocking drugs in this situation is that, by antagonizing sympathetic vasoconstrictor tone (particularly at the venous end of the capillary bed), they increase peripheral tissue perfusion. Perlroth & Harrison (1969) have, however, questioned the value of α-adrenoceptor blocking drugs in cardiogenic shock on the grounds that, by lowering diastolic pressure, they may reduce coronary perfusion in patients with an exaggerated left ventricular end-diastolic pressure or with a ' fixed ' coronary vascular resistance, a situation where perhaps autoregulation is absent.

Recently Gould (Gould, 1969 ; Gould, Zahir & Ettinger, 1969) has drawn attention to the cardiac stimulation which results from the administration of fairly small doses of phentolamine. This can lead to an increased cardiac output and to peripheral vasodilatation without marked systemic hypotension, a situation which might well improve, rather than reduce, myocardial tissue perfusion. There is in fact evidence that, in normotensive animals, phentolamine increases myocardial blood flow (Grayson & Mendel, 1961).

This report describes the effects of infusions of phentolamine, in amounts smaller than those required to produce any significant degree of α-adrenoceptor blockade, on myocardial contractility and blood flow.

Methods

Twenty-five cats of both sexes weighing between 1·3 and 4·5 kg were anaesthetized with sodium pentobarbitone (30 mg/kg i.p.). Temperature was measured from the rectum, mid-oesophagus and (occasionally) the aortic arch using direct recording thermocouples (Ellab, Copenhagen). Body (mid-oesophageal) core temperature was maintained between 36·5 and 38° C. After tracheotomy the animals were artificially respired with room air delivered by a Palmer positive pressure ventilation pump (stroke volume 45–75 ml; rate 20/min). The stroke volume was adjusted so that the arterial P_{O_2}, measured using a micro-electrode system (Radiometer, Copenhagen), was between 70 and 100 mmHg (1mmHg≡1·333 mbar). At a pH of 7·350–7·400 this indicates an arterial blood oxygen saturation of between 85 and 100% (Bartels & Harms, 1959). Arterial blood P_{O_2}, P_{CO_2}, pH, haemoglobin and PCV were monitored throughout the experiment.

Systemic arterial pressure was recorded from either a femoral or carotid artery using a capacitance transducer (Elema-Schönander EMT 35). In some experiments the descending aortic pressure trace was continuously differentiated using a circuit similar to that described by Schaper, Lewi & Jageneau (1965). Right atrial pressure was recorded using a second capacitance transducer (Elema-Schönander EMT 33) from a catheter inserted via the right external jugular vein. Left ventricular pressure was measured using a third transducer (Elema-Schönander EMT 34) and a steel catheter inserted by way of the right carotid artery or by direct left ventricular puncture. The left ventricular pressure pulse was continuously differentiated to provide an index of myocardial contractility and end-diastolic pressure (LVEDP) was measured by cutting off the intraventricular pressure pulse above 20 mmHg (McInnes & Parratt, 1969). Left ventricular pressure, LVEDP, left ventricular or descending aortic dp/dt, systemic arterial pressure, right atrial pressure and the electrocardiogram (leads I or II) were recorded on an eight-channel ink jet writing recorder (Mingograph 81).

Myocardial blood flow was measured by a heat clearance technique. The full experimental details and the methods used to calculate myocardial thermal conductivity increment (an index of local blood flow around the implanted recorder: Grayson & Mendel, 1961; Grayson & Parratt, 1966) and 'corrected temperature' (an index of local myocardial metabolic heat production: Dosekun, Grayson & Mendel, 1960; Parratt, 1969) have been described by McInnes & Parratt (1969).

In three of the later experiments cardiac output was measured by thermal dilution (Hosie, 1962). A 36 s.w.g. copper-constantan junction was inserted by way of the right femoral artery into the descending portion of the arch of the aorta; the cold (reference) junction, together with a direct recording thermocouple (Ellab, Copenhagen) was in the rectum. The output from the thermocouple circuit was fed directly into a Kipp & Zonen BD5 recorder (50 μV 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 thermal dilution curve calculated by the method of Williams, O'Donovan & Wood (1966).

Phentolamine (Rogitine, Ciba) was infused into a femoral vein using a Sage slow infusion pump. The dose required to stimulate the myocardium and to increase myocardial blood flow varied in individual animals but was usually between (5 and

50 μg/kg)/minute. Each infusion was given for 5 min and, for comparison, infusions of adrenaline and noradrenaline ((1·0 μg/kg)/min) were given before and after each phentolamine dose.

Results

A total of thirty-two infusions of phentolamine ((5, 10, 20 or 50 μg/kg)/min) were given and the effects are summarized in Table 1. The main point that emerged from these results was that phentolamine markedly increased left ventricular *dp/dt* max (by 29–45%) without increasing LVEDP. This, together with the cardiac output data which were available in three of the animals, is indicative of an increase in myocardial contractility. Heart rate, pulse pressure and the rate of rise of the central aortic pressure pulse were increased and systolic ejection time was consistently reduced. There was no consistent effect on left myocardial blood flow with a dose of (10 μg/kg)/min, but a definite increase with a dose of (20 μg/kg)/minute. This change of blood flow was accompanied by increases in 'corrected temperature', an index of left myocardial metabolic heat production, ranging from +0·01 to +0·06° C (mean increase; six experiments, +0·04° C). In the cats in which cardiac output was measured the mean value after thoracotomy was 370±31 ml/minute. In these experiments phentolamine ((50 μg/kg)/min) increased cardiac output by a mean of 14%, an effect not completely accounted for by the increase in heart rate.

Although each of the above changes was invariably observed, there was a considerable variation in the timing and duration of the effects. There were four main kinds of response, three of which are illustrated in Figs. 1 and 2.

1. In some experiments (particularly with smaller doses of phentolamine) a slight increase in systolic arterial pressure was observed during the period of infusion

TABLE 1. *Cardiovascular effects of intravenous infusions of phentolamine ((10–50 μg/kg)/min for 5 min) in cats anaesthetized with pentobarbitone*

		Change from control (mean±S.E. of mean) induced by phentolamine ((μg/kg)/min)		
		10	20	50
Number of observations	Control	(6)	(16)	(6)
Systolic blood pressure (mmHg)	146±3	−2±3	−7±3	−10±4
Diastolic blood pressure (mmHg)	100±3	−5±4	−12±2	−13±5
Descending aortic *dp/dt* (mmHg/s)	2654±427	+742±103	+856±236	+400
Heart rate (beats/min)	205±7	+6±4	+15±2	+15±4
Systolic ejection time (ms)	120±7	−11±6	−6±3	−10±4
Left ventricular systolic pressure (mmHg)	140±6	−13*	0*	+12±2
Left ventricular end-diastolic pressure (mmHg)	7·2±0·8	−2*	−0·8±1·0	−0·1±0·9
Left ventricular *dp/dt* max (mmHg)	4283±387	+1400*	+1244±454	+1929±459
Myocardial blood flow (thermal conductivity increment, c.g.s. units×10^{-4})	5·9±0·8†	+4% (−15 to +31)	+20% (+14 to +29)	– –
Myocardial metabolic heat production (corrected temp., °C)	–	<+0·01*	+0·04	

* Three-four experiments only. † (5·9±0·8)×10^{-4}×418·68 Jm/m^2s °C.

without a marked effect on diastolic pressure (the first phentolamine response in Fig. 1). The increase in myocardial blood flow and in aortic dp/dt were maintained throughout the infusion and returned to control levels when the infusion was terminated.

2. With larger doses ((20–50 μg/kg)/min) decreases in systolic, and particularly in diastolic, blood pressures occurred together with a widening of the pulse pressure (Fig. 2).

3. In many of the experiments, the increases in heart rate and in left ventricular dp/dt max were maintained after terminating the infusion. This is clear from both Figs. 1 and 2. Thus, in the experiment illustrated in Fig. 2, the heart rate was increased from 213 to 256 beats/min by the first infusion of phentolamine ((50 μg/kg)/min) and was still at this level when the second infusion was commenced over 40 min later. It was also clear from these experiments that the heart rate increased whatever the direction or magnitude of the blood pressure change and was therefore not a reflex response to systemic hypotension.

4. In two of the animals (that is in about 10% of the experiments) tachycardia and increased left ventricular dp/dt max were not observed with any dose of phentolamine, despite the usual decreases in systemic arterial pressure. In view of our final conclusion regarding the mode of action of phentolamine, it was of interest that one of these two animals had a low initial systemic arterial pressure (100/64 mmHg) and heart rate (132 beats/min). An infusion of phentolamine ((20 μg/kg)/min) decreased systolic and diastolic pressures by 12 mmHg. Heart rate and aortic dp/dt were unchanged.

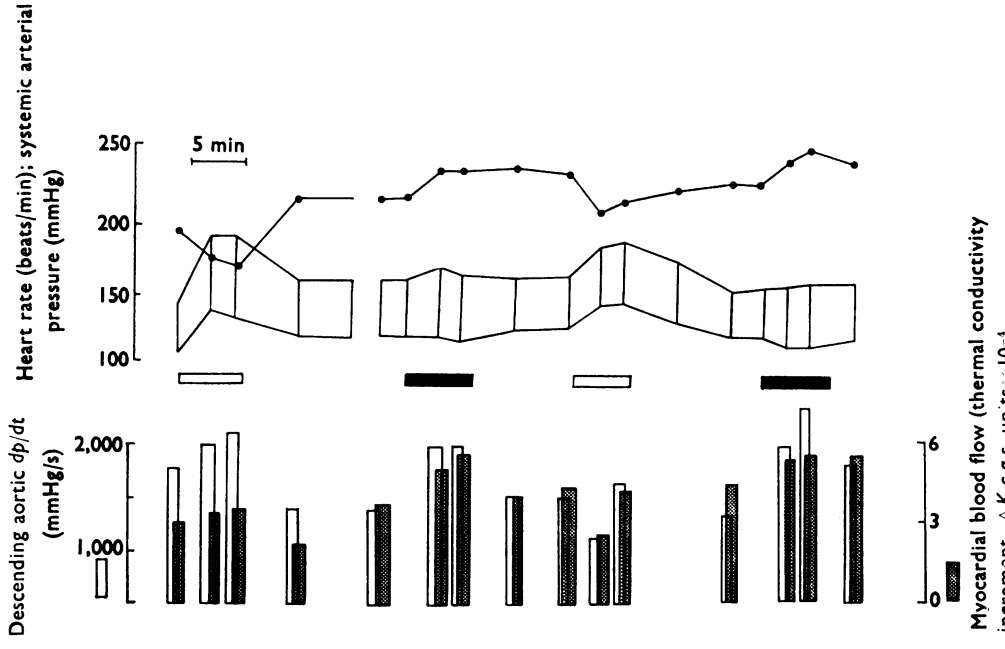

FIG. 1. Effect of infusions of phentolamine ((10 and then 20 μg/kg)/min—at the solid horizontal bars) and of noradrenaline ((1·0 μg/kg)/min—at the open horizontal bars) on heart rate (beats/min), systemic arterial blood pressure (mmHg), aortic dp/dt max (mmHg/s—open columns) and myocardial blood flow (as δk, thermal conductivity increment, c.g.s. units $\times 10^{-4}$ —hatched columns). Time scale 5 minutes.

There were clearly similarities between the cardiovascular effects of phentolamine and of catecholamines and there were several indications that phentolamine might be acting by releasing adrenaline or noradrenaline or by preventing their tissue uptake. Experiments were therefore performed to test this hypothesis. In four cats the effects of phentolamine infusions were examined before and after alprenolol, a β-adrenoceptor blocking agent, in a dose (0·5 mg/kg) previously found markedly to reduce the cardiovascular effects of infused catecholamines (Parratt & Wadsworth, 1970). The results are summarized in Table 2. The effects of phentolamine on heart rate, *dp/dt* max, cardiac output and systolic ejection time were greatly reduced following β-adrenoceptor blockade, whereas the effect on systemic arterial pressure

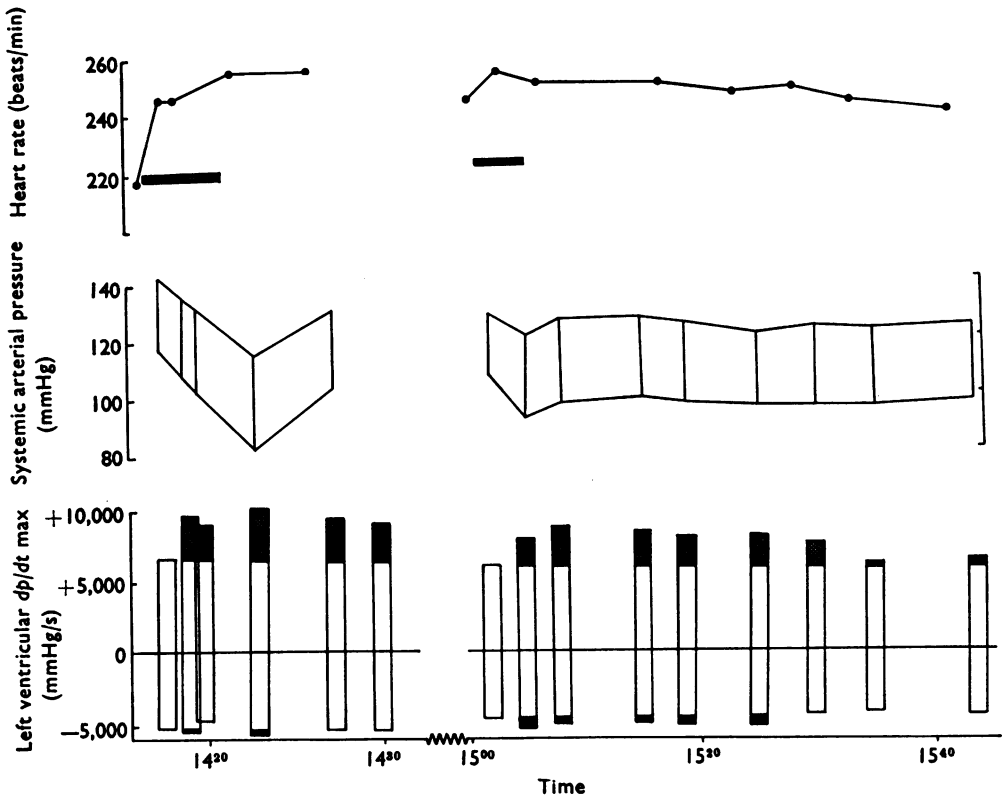

FIG. 2. Effect of infusions of phentolamine ((50 μg/kg)/min—at the horizontal bars) on, heart rate (beats/min), systemic arterial blood pressure (mmHg) and left ventricular *dp/dt* (mmHg/s). The hatched areas on the vertical columns represent the increase in *dp/dt* max (+ve and −ve) induced by phentolamine.

TABLE 2. *Changes in systolic and diastolic blood pressures (SBP, DBP mmHg), heart rate (HR, beats/min), left ventricular* dp/dt *max (mmHg/s) and systolic ejection time (SET, ms) induced by infusions of phentolamine ((50 μg/kg)/min) in anaesthetized cats, before and after alprenolol (0·5 mg/kg)*

	Before alprenolol					After alprenolol				
Expt.	SBP	DBP	HR	LV*dp/dt*	SET	SBP	DBP	HR	LV*dp/dt*	SET
1	−22	−32	+18	+2,900	−22	−8	−10	0	+200	0
2	−18	−18	+22	+1,270	-	−16	−20	−5	−200	-
3	−8	−16	+10	+1,913	−8	−14	−14	+2	+354	−4
4	−10	−12	+8	+400*	−2	−12	−18	0	0*	0

* Descending aortic *dp/dt*.

was largely unaltered. Recovery from blockade by alprenolol (Fig. 3) was rather slower than that observed with catecholamines (Parratt & Wadsworth, 1970).

In a further three cats the effects of phentolamine were studied before and after bretylium (5 mg/kg, i.v.). Bretylium itself, after initial sympathomimetic effects, decreased blood pressure, heart rate and left ventricular dp/dt max. That these effects were so marked was probably due to increased cardiac sympathetic support which results from pentobarbitone anaesthesia (see Pitt, Green & Sugishita, 1970). In no experiment did phentolamine increase heart rate or left ventricular dp/dt max after bretylium. A further two cats were pretreated with reserpine (1·0 mg/kg, 24 h previously). In neither cat was there any suggestion of myocardial stimulation after the administration of intravenous infusions of phentolamine.

Discussion

The results confirm the finding of Gould *et al.* (1969) in the dog and in man that phentolamine increases myocardial contractility. The evidence that this is so from the present experiments is that the drug increased left ventricular dp/dt (without an increase in end-diastolic pressure) and aortic dp/dt as well as cardiac output and myocardial metabolic heat production. These effects were accompanied by increases

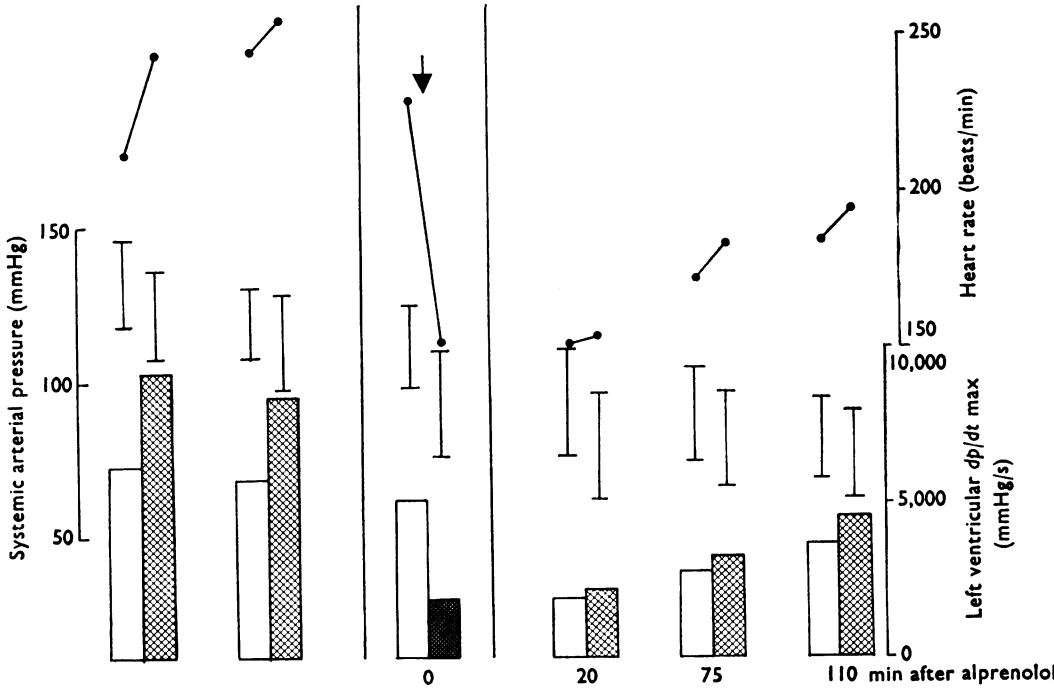

FIG. 3. Effect of alprenolol (0·5 mg/kg—at the arrow) on the heart rate, systemic arterial pressure and left ventricular dp/dt responses to phentolamine ((50μg/kg)/min). The control values (open columns) are given on the left of each group of observations and the values after phentolamine (shaded columns) are on the right of each group. The direct effect of alprenolol is shown between the two vertical lines. Before β-adrenoceptor blockade phentolamine increased heart rate, pulse pressure and left ventricular dp/dt max. These effects were largely prevented by alprenolol but there was some recovery of the phentolamine responses over a period of 2 hours.

in myocardial blood flow. Although a direct vasodilator effect on the myocardial blood vessels cannot be ruled out, the more likely explanation for the increased myocardial tissue perfusion is that it is secondary to increased cardiac work and the resultant changes in metabolism and oxygen demand. Whether or not cardiac stimulation is seen probably depends upon the dose of phentolamine used. These experiments have demonstrated cardiac stimulation with fairly small doses; there was no evidence of such stimulation when larger doses of phentolamine (0·5–2·0 mg/kg) were used (Das & Parratt, unpublished observations) and when the main effect was a marked decrease in systemic blood pressure resulting from a direct effect on vascular smooth muscle together with a degree of α-adrenoceptor blockade.

There are several possible explanations for phentolamine-induced myocardial stimulation. It could result from a direct positive inotropic effect on cardiac muscle or could involve the sympathetic nervous system, either reflexly (as a result of systemic hypotension), centrally (on neurones within the central nervous system) or directly (on the efferent sympathetic nerve or at the receptor level). The evidence from the present experiments is that phentolamine increases myocardial contractility by an effect involving the sympathetic nervous system. With the exception of the action on systemic blood vessels (which is probably a direct effect of the drug on vascular smooth muscle) all the cardiovascular responses of phentolamine mimic those of β-adrenoceptor stimulation. There were increases in heart rate, cardiac output, left ventricular and descending aortic dp/dt max, myocardial blood flow and myocardial metabolic heat production. These effects were not seen in animals treated with reserpine, bretylium or the β-adrenoceptor blocking drug, alprenolol.

This study does not permit further clarification concerning the mechanisms by which the sympathetic nervous system is involved after phentolamine administration. The intravenous injection of phentolamine in man (in a similar dose to that used in the present study) resulted in tachycardia and a markedly increased cardiac output (Taylor, Sutherland, MacKenzie, Staunton & Donald, 1965). The conclusion reached by these authors was that there was a reflex response from carotid baroceptors leading to tachycardia, peripheral vasoconstriction and an increase in cardiac output. In some of the present experiments, however, increases in left ventricular dp/dt max occurred with only minimal effects on systolic blood pressure (2–5 mmHg; Table 1); on occasions (as in Fig. 1) small doses of phentolamine increased systolic pressure and still markedly increased aortic dp/dt. It would seem therefore that some other factor is implicated. This might involve sensitization of carotid baroceptors (Walker, Heymans, Wilson & Richardson, 1950; Martini & Rovati, 1954), increased release of noradrenaline from nerves, or inhibition of noradrenaline uptake. There is indeed some evidence that both these can occur (Brown, Davies & Ferry, 1961 ; Gillespie & Kirpekar, 1965 ; Kirpekar & Cervoni, 1963 ; Iverson, 1967) although in doses very much greater than those required to stimulate the myocardium *in vivo*.

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