Effect of propranolol on hypoxia induced myocardial vasodilatation

I. McA. Ledingham, J. R. Parratt* and J. P. Vance, *Hyperbaric Unit, University Department of Surgery (Western Infirmary) and Department of Pharmacology, University of Strathclyde, Glasgow*

On the basis that sotalol markedly reduced, or even reversed, the coronary vasodilatation which results from systemic hypoxia in open chest dogs, Folle & Aviado (1965) suggested that β-adrenoceptor blocking drugs in general might seriously interfere with the self-regulating control of myocardial oxygen supply in patients with coronary artery disease. This conclusion clearly has far reaching implications and, since the experimental procedures used by these authors involved considerable surgery, it seemed important to re-examine the effects of β-adrenoceptor blockade on the responses of the myocardial vessels to a decreased arterial oxygen tension.

Anaesthesia was induced in seven dogs with intravenous sodium thiopentone and, after endotracheal intubation, was maintained using 0·5–1·0% trichlorethylene. Under fluoroscopic control, catheters were placed in the coronary sinus, right atrium, descending aorta and either the circumflex or the anterior descending branch of the left coronary artery. Myocardial blood flow was measured using a ^{133}xenon clearance technique (Ross, Ueda, Lichtlen & Rees, 1964; Ledingham, McBride, Parratt & Vance, 1970) with the scintillation counter placed over the praecordium. Hypoxaemia induced by rapidly reducing the inspired oxygen content to 10–11% (arterial pO_2 27 mmHg) increased myocardial blood flow [from (119±10 to 184±8 ml/100g)/min] and mean systemic blood pressure (112±5 to 133±10 mmHg), decreased heart rate (139±10 to 122±11 beats/min) and myocardial vascular resistance and had no significant effect on myocardial oxygen consumption [(10·3±0·8 to 9·6±1·4 ml/100g)/min]. Although a combination of propranolol (0·2 mg/kg) and atropine (0·04 mg/kg) markedly decreased each of these parameters, the cardiovascular responses to hypoxia were essentially unaltered by these drugs. Thus myocardial blood flow was increased by hypoxia from (89±10 to 158±9 ml/100g)/min and mean blood pressure from 96±8 to 117±8 mmHg. Heart rate and myocardial vascular resistance were again reduced. These results indicate that coronary vasodilatation, under our conditions of hypoxia, is due to an effect of the lowered oxygen tension (or the release of some vasodilator metabolite) on vascular smooth muscle and there is no support for the contention of Folle & Aviado (1965) that β-adrenoreceptor blocking drugs interfere with hypoxic induced coronary vasodilatation.

REFERENCES

Folle, L. E. & Aviado, D. M. (1965). Cardiovascular effects of anoxia and the influence of a new beta adrenergic receptor blocking drug. *J. Pharmac. exp. Ther.*, **149**, 79–90.

Ledingham, I. Mc.A., McBride, T. I., Parratt, J. R. & Vance, J. P. (1970). The effect of hypercapnia on myocardial blood flow and metabolism. *J. Physiol., Lond.*, **210**, 87–105.

Ross, R. S., Ueda, K., Lichtlen, P. R. & Rees, J. R. (1964). Measurement of myocardial blood flow in animals and man by selective injection of radioactive inert gas into the coronary arteries. *Circulation Res.*, **15**, 28–41.

Effects of β-adrenoceptor blocking drugs on the chronotropic and inotropic actions of isoprenaline on the acutely denervated dog heart

J. D. Harry*, C. T. Kappagoda, R. J. Linden and H. M. Snow, *Cardiovascular Unit, Department of Physiology, University of Leeds*

The effect of β-adrenoceptor blocking drugs on the dog heart is well known (e.g.

Shanks, 1966). However, the interpretation of this effect is difficult because in many instances the heart has been under the influence of cardiac reflexes. The present investigation reports the actions of propranolol, oxprenolol and practolol on the acutely denervated dog heart.

Dogs were anaesthetized with pentobarbitone sodium (30 mg/kg intravenously), artificially respired and the chest opened in the mid line. The maximum rate of change of pressure in the left ventricle (*dP/dt* max) was used as an index of the inotropic state in a preparation in which heart rate and mean aortic pressure were held constant (Furnival, Linden & Snow, 1970). The experimental design consisted of infusing isoprenaline at increasing rates, and measuring free heart rate and *dP/dt* max at a constant heart rate and at a constant mean aortic arterial pressure for each isoprenaline rate before and in the presence of the β-adrenoceptor antagonist. Measurements were made in the steady state situation. From these measurements linear relationships were obtained between free heart rate and *dP/dt* max, in the absence and in the presence of the blocking drug.

Each blocking drug was tested in three dogs. In each of the nine experiments, in the presence of the blocking drug, isoprenaline caused a smaller response in *dP/dt* max for a given change in heart rate. It is convenient to express the results as a change in *dP/dt* max for a given change in heart rate produced by isoprenaline. The range of heart rate selected was 150–180 beats/min, in the middle range of the dose-response curve. The changes in *dP/dt* max are shown in Fig. 1.

Thus propranolol, oxprenolol and practolol are qualitatively the same in this preparation against the agonist isoprenaline. Two interpretations of these results are possible. (1) Each of these drugs has a negative inotropic action on the denervated dog heart over and above their β-adrenoceptor blocking activity. (2) Adrenoceptors in the sino-atrial node behave differently to those in cardiac muscle.

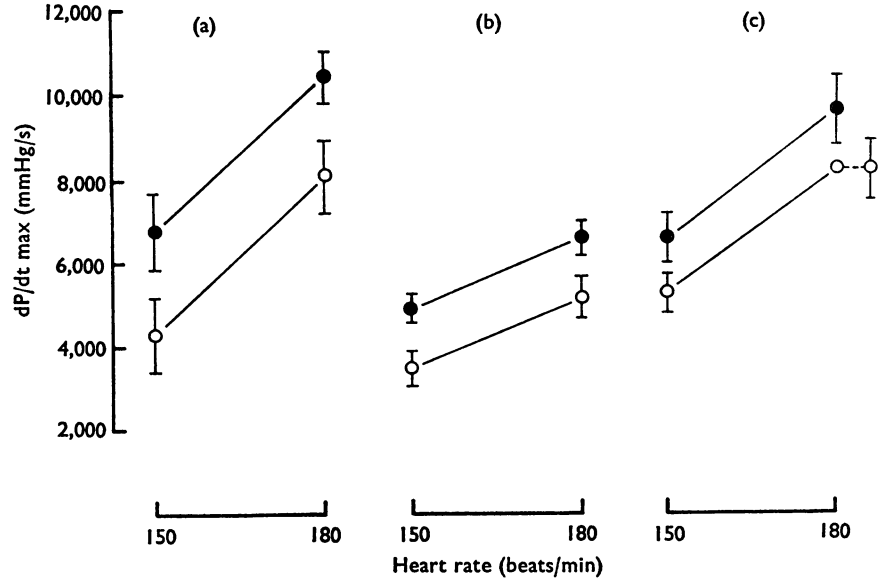

FIG. 1. Changes in *dP/dt* max with the heart rate for (a) propranolol (0·04–0·8 mg/kg) (b) oxprenolol (0·04–0·32 mg/kg) and (c) practolol (0·4–2·0 mg/kg). Closed circles are controls; open circles are drug treated.

This work is supported by grants from the British Heart Foundation, the Medical Research Council and the Wellcome Trust.

REFERENCES

FURNIVAL, C. M., LINDEN, R. J. & SNOW, H. M. (1970). Inotropic changes in the left ventricle; the effect of changes in heart rate, aortic pressure and end-diastolic pressure. *J. Physiol., Lond.*, in the Press.

SHANKS, R. G. (1966). The pharmacology of beta-sympathetic blockade. *Am. J. Cardiol.*, **18**, 308–316.

Adrenoceptors mediating metabolic responses in the greyhound

J. G. KELLY* and R. G. SHANKS, *Department of Therapeutics and Pharmacology, The Queen's University and Department of Pharmacy, College of Technology, Belfast, Northern Ireland*

Studies on the metabolic effects of catecholamines have suggested that the receptors mediating liver and muscle glycogenolysis and lipolysis in the dog are β-receptors (Mayer, Moran & Fain, 1961). Not all species behave similarly, as liver glycogenolysis is mediated by α-receptors in the rat (Fleming & Kenny, 1964) and in man (Antonis, Clark, Hodge, Molony & Pilkington, 1967). Recently, Lands, Arnold, McAuliff, Luduena & Brown (1967) have suggested that β-adrenoceptors could be divided into two groups, $\beta 1$ and $\beta 2$. This classification has been supported by the development of drugs such as salbutamol, which mainly stimulates $\beta 2$ adrenoceptors (Cullum, Farmer, Jack & Levy, 1969), and practolol, which selectively blocks $\beta 1$ adrenoceptors (Dunlop & Shanks, 1968). The subdivisions of β-adrenoceptors mediating the metabolic responses to catecholamines have not been investigated using these two drugs.

The present work examines some of the metabolic responses to isoprenaline, salbutamol and phenylephrine in the dog and the effects of propranolol and practolol on these responses to isoprenaline. A series of increasing doses of isoprenaline, phenylephrine and salbutamol were given as 10 min intravenous infusions to greyhounds anaesthetized by intravenous injection of pentobarbitone (30 mg/kg). Heart rate was recorded and blood samples were analysed for free fatty acids, lactic acid and glucose. In the experiments in which phenylephrine was given, arterial pressure was recorded.

Phenylephrine in doses sufficient to cause an appreciable increase in arterial pressure did not elevate any of the metabolic parameters but isoprenaline increased heart rate, free fatty acid, lactic acid and glucose concentrations. Salbutamol increased heart rate, fatty acid and glucose concentrations having activities relative to isoprenaline of 1/30, 1/10 and 1/1, respectively. Minimal increases in lactic acid were produced by salbutamol.

Intravenous administration of propranolol reduced the heart rate and metabolic responses to isoprenaline to the same extent. Practolol (3 mg/kg), reduced heart rate and free fatty acid responses to isoprenaline but did not significantly alter lactic acid or glucose responses. Practolol (9 mg/kg), caused significant reduction of the lactic acid response although it did not affect the glucose response.

The above results are consistent with the hypothesis that the receptors mediating lipolysis and muscle glycogenolysis in the dog are similar to those for heart rate, that is, $\beta 1$, while the receptors mediating liver glycogenolysis are $\beta 2$.

REFERENCES

ANTONIS, A., CLARK, M. L., HODGE, R. L., MOLONY, M. & PILKINGTON, T. R. E. (1967). Receptor mechanisms in the hyperglycaemic response to adrenaline in man. *Lancet*, **1**, 1135–1137.