Cardio-selective β-adrenoceptor blockade and the coronary circulation

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After blockade of myocardial, but not coronary vascular β-adrenoceptors by practolol, cardiac sympathetic stimulation or exogenously administered noradrenaline gave rise to coronary vasoconstriction, possibly due to stimulation of coronary α-adrenoceptors.

The decrease in coronary vascular resistance that normally accompanies the chronotropic and inotropic effects of sympathetic nerve stimulation or administration of catecholamines, thereby satisfying the increased myocardial oxygen requirement, converts to an increase in the presence of propranolol (Feigl, 1967; Gaal, Kattus, Kolin & Ross, 1966). Since this increase in coronary resistance might occur in patients undergoing propranolol therapy (Parratt, 1967), the suggestion by Parratt & Wadsworth (1970) that release of myocardial catecholamines would not be expected to give rise to coronary vasoconstriction after practolol, a cardio-selective β_1-adrenoceptor antagonist (Dunlop & Shanks, 1968), warranted investigation. The reasoning behind Parratt and Wadsworth's suggestion was not apparent, but might be that the decrease in coronary resistance induced by catecholamines is due to a direct stimulation of coronary vascular β-adrenoceptors rather than being the indirect result of the chronotropic and inotropic effects of catecholamines.

It was against this background that it was decided to study the effects of practolol on coronary vascular resistance, using the open-chest dog.

Methods.—Beagles (three male, three female) weighing 11–12·5 kg were anaesthetized with sodium pentobarbitone (30 mg/kg i.v.). Polyethylene catheters were inserted into the descending aorta and into the left ventricle to record systemic arterial pressure and left ventricular pressure, respectively. The rate of rise of left ventricular pressure (dp/dt) was obtained by differentiation using an EAL analogue computer. Heart rate was also recorded.

The chest was opened through the fifth left intercostal space and ventilation maintained artificially using room air. The pericardium was incised, a length (1–1·5 cm) of the left circumflex coronary artery cleared, and a calibrated electromagnetic flow probe placed around it. Zero flow reference was obtained by occlusion of the artery distal to the flow probe. The resistance of the coronary bed supplied by the left circumflex coronary artery was derived instantaneously using the analogue computer. The left stellate ganglion was stimulated supramaximally (20 V, 0·5 ms, 24 Hz for periods of 30 s), by means of shielded platinum wire electrodes inserted through a stab incision in the chest wall. All drugs were administered via a polyethylene catheter inserted into the right femoral vein. The ganglion was stimulated or catecholamines administered at 10 min intervals, commencing 5 min after each dose of practolol, the total interval between doses of practolol being 45 min.

Results were calculated as the mean of three cardiac cycles during control periods and at the point of maximal myocardial contractile response. The time taken to reach peak contractility after either catecholamine administration or stellate ganglion stimulation gave a reference point for measuring coronary responses after the increases in contractility had been abolished by practolol. Measurements of coronary flow and resistance were made at the end diastole. Results are expressed as the mean $\pm$S.E. for six dogs unless otherwise stated.

Results.—1. *Direct cardiovascular effects of practolol.* Practolol (5 mg/kg) caused a significant ($P<0·02$) reduction in systolic blood pressure in five dogs, arterial pressure being reduced from $168\pm10/105\pm7$ to $151\pm8/94\pm7$ mmHg (1 mmHg$\equiv$1·333 mbar). Bradycardia occurred in five dogs, mean heart rate falling from 153 ± 10 to 136 ± 9 beats/min. A significant ($P<0·05$) reduction in myocardial contractility, assessed as the maximum rate of rise of left ventricular pressure (dp/dt max.) occurred in five dogs, the mean reduction being $16\pm8\%$. Coronary vascular resistance was increased by $9·3\pm2·1\%$ ($P<0·05$) and coronary flow reduced by $20\pm7\%$ ($P<0·05$).

Four of the six dogs were given practolol (20 mg/kg) after the effect of 5 mg/kg had been determined. This caused no further changes in blood pressure or heart rate. Myocardial contractility however, was further decreased in three dogs, the mean reduction in the four dogs being $10 \pm 7\%$. Coronary vascular resistance was further increased by $9{\cdot}9 \pm 2{\cdot}9\%$ and coronary blood flow further reduced by $12 \pm 4\%$, in the four dogs. These changes are calculated as percentages of values obtained immediately before the administration of practolol (20 mg/kg).

2. *Effects of practolol on responses to left stellate ganglion stimulation and to intravenous noradrenaline.* Stimulation of the left stellate ganglion or administration of noradrenaline (2·5 μg/kg), caused an increase in systemic blood pressure, dp/dt max. and, in most cases, a small increase in heart rate. Coronary resistance was markedly reduced (Fig. 1). These changes resulted in an increase in coronary blood flow.

After practolol (5 mg/kg), the increases in dp/dt and heart rate were either abolished or markedly reduced, while the increases in blood pressure were not affected. Coronary resistance was increased (Fig. 1) and the coronary flow responses were either diminished or eliminated.

Increasing the dose of practolol to 20 mg/kg abolished the myocardial contractile response to stellate stimulation and to noradrenaline, and the coronary resistance was further increased (Fig. 1). In one dog, a small increase in coronary flow persisted, probably due to an exceptionally large increase in perfusion pressure.

3. *Effects of practolol on responses to intravenous adrenaline.* The changes caused by adrenaline (2·5 μg/kg) resembled those due to noradrenaline or stellate stimulation. Practolol (5 mg/kg) either abolished or markedly reduced the increases in heart rate and dp/dt max., but had no effect on the pressor response. A small increase in coronary resistance occurred in one dog while the responses in the other five dogs were reduced. Coronary flow increases were only slightly diminished. There were no further significant effects when the dose of practolol was increased to 20 mg/kg.

4. *Effects of practolol on responses to intravenous isoprenaline.* The myocardial responses to isoprenaline (0·5 μg/kg) resembled those responses to adrenaline, noradrenaline and stellate stimulation, and were accompanied by a fall in systemic blood pressure. Practolol (5 mg/kg) abolished or markedly reduced the tachy-

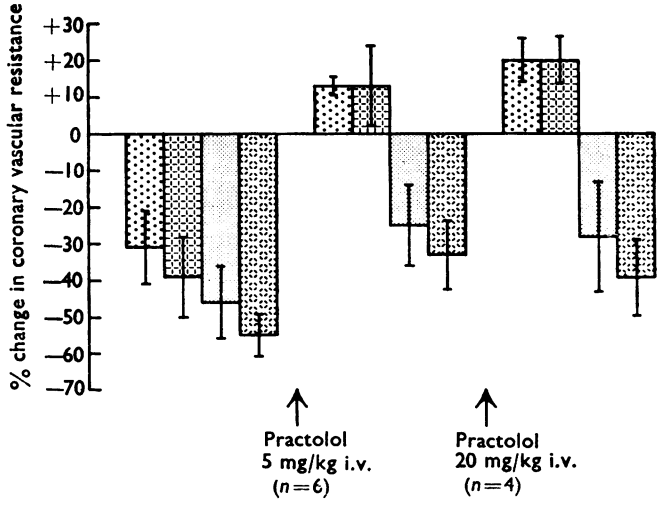

FIG. 1. Effect of practolol on the changes in coronary vascular resistance induced by left stellate ganglion stimulation (20 V, 0·5 ms, 24 Hz), noradrenaline (2·5 μg kg), adrenaline (2·5 μg/kg) and isoprenaline (0·5 μg/kg) in anaesthetized dogs. Each column represents the mean percentage change ± S.E. from values measured immediately before the response. ⬚, Stellate ganglion stimulation; ⬚, noradrenaline; ⬚, adrenaline; ⬚, isoprenaline.

cardia and the increase in contractility, but did not affect the vasodepression. The fall in coronary resistance was only slightly diminished (Fig. 1). Although practolol (20 mg/kg) reduced the depressor response in two dogs, the fall in coronary resistance was not markedly altered (Fig. 1).

5. *Effects of phentolamine after practolol.* Administration of phentolamine (2·5 mg/kg) after practolol (20 mg/kg) caused a slight fall in blood pressure and heart rate, and an increase in coronary vascular resistance. The pressor responses to adrenaline were reversed, those to noradrenaline and stellate stimulation were abolished and the increases in coronary resistance produced by noradrenaline and stellate stimulation reverted to decreases.

Discussion.—The above results are in agreement with those recently published by Ross & Jorgensen (1970), who found that practolol, in amounts which blocked the increase in myocardial contractile force, did not affect the direct coronary dilator action of isoprenaline, but reduced or reversed the dilator effects of adrenaline and noradrenaline. Our observations agree with their suggestion that the coronary vascular β-adrenoceptors are more resistant to blockade with practolol than are the β_1-adrenoceptors of the myocardium.

The doses of practolol used in the present experiments blocked the increases in heart rate and force resulting from stimulation of the cardiac sympathetic nerves or from administration of catecholamines. Since the coronary vasodilator responses to isoprenaline and adrenaline were not significantly altered by increasing the dose of practolol, it is likely that such doses did not affect the responsiveness of the coronary vascular β-receptors. Under these conditions, the direct effects of the sympathomimetic amines on the coronary vasculature are presumably observed, and neuronally-released or exogenous noradrenaline invariably caused an increase in coronary vascular resistance.

When the coronary vascular α-adrenoceptors are blocked with phentolamine, after the myocardial effects of sympathetic stimulation and noradrenaline have been abolished with practolol, sympathetic stimulation and noradrenaline once again cause decreases in coronary vascular resistance. This implies that the coronary vasoconstriction is a result of α-adrenoceptor stimulation, and also provides further evidence that the coronary vascular β-adrenoceptors are not blocked by practolol.

We therefore suggest that coronary vasoconstriction will occur during sympathetic stimulation in the presence of myocardial β_1-adrenoceptor blockade, whether or not coronary vascular β-adrenoceptors have been blocked.

Practolol was kindly supplied by I.C.I. Ltd.

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(*Received September* 17, 1970)