Effect of intracoronary and intravenous propranolol on human coronary arteries

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The effect of intracoronary and intravenous propranolol on coronary vasomotion was evaluated in 28 patients with coronary artery disease. Luminal area of a normal and a stenotic coronary vessel segment was determined at rest, during submaximal bicycle exercise and 5 min after 1·6 mg sublingual nitroglycerin administered at the end of the exercise test involving biplane quantitative coronary arteriography. Patients were divided into three groups: group 1 (n = 12) served as the control group, group 2 consisted of 10 patients with intracoronary administration of 1 mg propranolol and group 3 of six patients with intravenous administration of 0·1 mg kg⁻¹ propranolol prior to the exercise text.

In the control group there was coronary vasodilation (+23%, P <0·01) of the normal and coronary vasoconstriction (−29%, P <0·001) of the stenotic vessel segment during bicycle exercise. After sublingual administration of 1·6 mg nitroglycerin there was vasodilation of ·both normal (+40%, P <0·001 vs rest) and stenotic (+12%, NS vs rest) vessel segments. In group 2 intracoronary propranolol was not accompanied by a change in coronary vessel area but both normal (+13%, P <0·05) and stenotic (+22%, P <0·05) vessel segments showed coronary vasodilation during bicycle exercise. After sublingual nitroglycerin there was further vasodilation of both normal (+31%, P <0·001 vs rest) and stenotic (+45%, P <0·01 vs rest) arteries. In group 3 intravenous administration of propranolol was associated with a decrease in coronary luminal area of both normal (−24%, P <0·001) and stenotic (−31%, P <0·001) vessel segments. During dynamic exercise there was coronary vasodilation of both vessel segments when compared with the data after intravenous injection of propranolol but there was no change in luminal area (normal vessel −2%, NS vs rest; stenotic vessel −3%, NS vs rest) when compared with the resting data. After sublingual administration of 1·6 mg nitroglycerin both normal (+21%, P <0·01) and stenotic (+36%, P <0·001) vessel segments showed coronary vasodilation.

It is concluded that supine bicycle exercise in patients with coronary artery disease is associated with vasodilation of the normal and vasoconstriction of the stenotic coronary arteries. Intravenous administration of propranolol is followed by coronary vasoconstriction of both normal and stenotic coronary arteries, probably due to secondary mechanisms because it is not observed after intracoronary injection of propranolol and it is overridden by bicycle exercise and sublingual nitroglycerin.

Introduction

Betablockers are frequently used in the treatment of patients with coronary artery disease

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and exercise-induced myocardial ischaemia. The beneficial effect of betablocking agents has been attributed to the reduction in myocardial oxygen consumption caused by a reduction in myocardial contractility, heart rate and left ventricular afterload. Previous studies have shown[1,2] that myocardial blood flow is decreased after

intravenous administration of propranolol, probably due to a decrease in coronary luminal area. Rafflenbeul and coworkers[3] reported a decrease in coronary luminal area of the large and the small epicardial arteries after intravenous administration of propranolol. It has been postulated that beta-adrenergic blockade potentiates coronary artery vasoconstriction by the unopposed alpha-adrenergic tone. These findings contrast with the well-documented beneficial effect of propranolol in the treatment of patients with coronary artery disease and classic angina pectoris in whom adverse reactions with potentiation of myocardial ischaemia are rare. Thus, the purpose of the present study was to examine the effect of intracoronary and intravenous propranolol on coronary vasomotion at rest and during supine bicycle exercise in patients with coronary artery disease.

Patients and methods

Twenty-eight patients (mean age 53 years, range 36 to 67 years) with coronary artery disease underwent coronary arteriography for diagnostic purposes (Fig. 1). Previous myocardial infarction was present in 17 patients and a positive exercise test with ST-segment depression $\geqslant 0.1$ mV and/or anginal pain in 26. All medication was stopped at least 12 to 24 h before cardiac catheterization. Patients were selected on a consecutive basis when the following criteria were fulfilled: a history of stable angina pectoris with no signs of coronary vasospasm and a clearly visible coronary artery stenosis for quantitative evaluation.

QUANTITATIVE CORONARY ARTERIOGRAPHY

After an interval of at least 10 min after the last diagnostic coronary arteriogram, baseline biplane coronary arteriography for quantitative evaluation was carried out after the patient's feet were attached to the bicycle ergometer[4,5]. Intracoronary injections of 5 to 7 ml of amidotrizoate (Urografin 76%) were used for quantitative coronary arteriography in the first group of patients, but later during the study 5 to 7 ml of iopamidol (Iopamiro 370) was injected for quantitative coronary arteriography to reduce the effect of the contrast medium on coronary vasodilation. Aortic and pulmonary
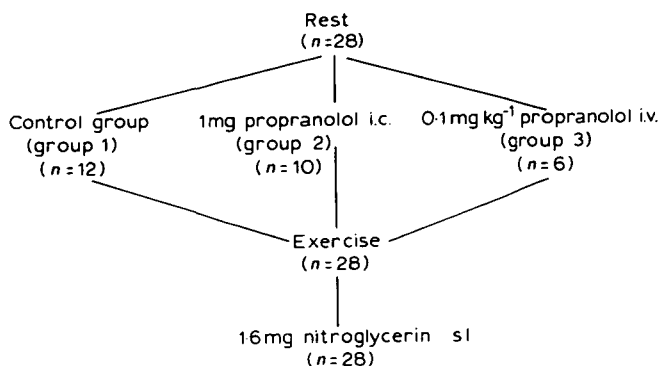

Figure 1 Study protocol for the assessment of coronary vasomotion in 28 patients with coronary artery disease and exercise-induced angina pectoris using biplane quantitative coronary arteriography. The control group consisted of 12 patients (group 1) with no pretreatment prior to the exercise test, group 2 of 10 patients with intracoronary administration of 1 mg propranolol prior to the exercise test and group 3 of six patients with intravenous administration of 0.1 mg kg^{-1} propranolol prior to the exercise test. The infusion of propranolol was carried out over 5 min; repeat coronary arteriography was performed after 6–8 min in group 2 and after 9–12 min in group 3. At the end of the exercise test 1.6 mg sublingual nitroglycerin was administered, and 5 min thereafter biplane coronary arteriography was repeated. i.c. = intracoronary, i.v. = intravenous, s.l. = sublingual.

artery pressure were recorded at rest and at the end of each exercise level immediately before coronary arteriography. Repeat coronary angiograms were obtained at the end of each exercise level which was begun at 50 to 75 W and was increased every 2 min in increments of 25 to 50 W. The exercise test was terminated because of anginal pain, fatigue or ST-segment depression of more than 0·2 mV. At the end of the exercise test 1·6 mg sublingual nitroglycerin was administered and biplane coronary arteriography was repeated 5 min thereafter. There were no complications related to the procedure in any of the 28 patients.
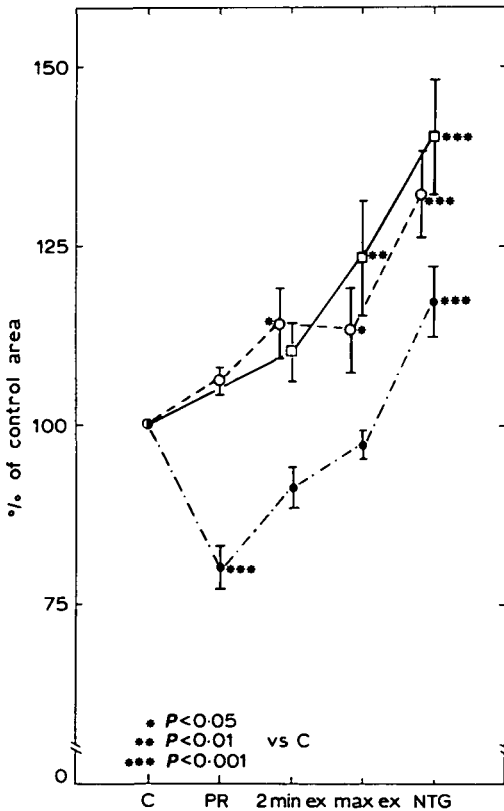
Quantitative evaluation of biplane coronary

Figure 2 Percent changes in normal coronary vessel segments during exercise in 12 control patients (□), 10 patients with intracoronary administration of 1 mg propranolol (O) and six patients with intravenous administration of 0·1 mg kg^{-1} propranolol (●). Data are given at rest (C), after intracoronary or intravenous administration of propranolol (PR), during 2 min of exercise (2 min ex.) and during maximal exercise (max ex.) as well as 5 min after 1·6 mg of sublingual nitroglycerin (NTG).
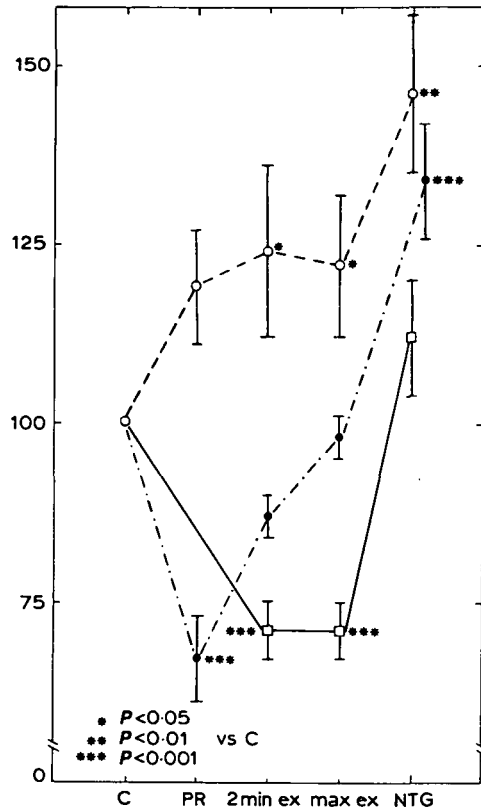

Figure 3 Percent changes in coronary stenosis area during exercise in 12 control patients (□), 10 patients with intracoronary administration of 1 mg propranolol (O) and six patients with intravenous administration of 0·1 mg kg^{-1} propranolol (●). Data are given at rest (C), after intracoronary or intravenous administration of propranolol (PR), during 2 min of exercise (2 min ex.), during maximal exercise (max ex.) as well as 5 min after 1·6 mg sublingual nitroglycerin (NTG).

arteriography was carried out in a blinded fashion. Tracings were made manually from both projections during diastasis or end-diastole. Each vessel segment was analysed four to six times separately and the results were averaged to reduce the sampling error[4,5]. A section of the catheter of known dimensions was traced as a scaling factor. The tracings of the coronary vessel segments were digitized manually and analysed on a PDP 11/34 computer[4,5]. The luminal area of a normal and a stenotic vessel segment was calculated in each patient and expressed in absolute values and in percent of the resting value (see Figs 2 and 3).

STATISTICS

Statistical comparisons of angiographic data in response to intracoronary or intravenous propranolol, supine bicycle exercise and sublingual nitroglycerin were carried out by a two-way analysis of variance for repeated measurements. Comparisons between all three groups were done by a one-way analysis of variance; when the analysis was significant the Scheffe test was applied. In both figures mean values ±1 standard error are given.

Results

HAEMODYNAMIC MEASUREMENTS

Administration of intracoronary propranolol was not associated with a significant change in heart rate (65 beats min^{-1} at rest and 64 beats min^{-1} after propranolol). However, after intravenous administration of propranolol heart rate decreased significantly ($P < 0.05$) from 76 beats min^{-1} at rest to 65 beats min^{-1} after propranolol. Mean aortic pressure remained unchanged after intracoronary or intravenous administration or propranolol (group 2, 97 mmHg at rest and 98 mmHg after propranolol; group 3, 104 mmHg at rest and 98 mmHg after propranolol). Heart rate increased significantly in all three groups during exercise, whereas mean aortic pressure showed a significant increase only in group 1, from 87 mmHg to 107 mmHg ($P < 0.001$) but remained unchanged in group 2 (97 vs 93 mmHg, NS) and group 3 (104 vs 113 mmHg, NS). Mean pulmonary artery pressure increased significantly from 26 mmHg to 47 mmHg ($P < 0.001$) in group 1, from 17 mmHg to 41 mmHg ($P < 0.001$) in group 2 and from 20 mmHg to 36 mmHg ($P < 0.001$) in group 3.

ANGIOGRAPHIC MEASUREMENTS

Percent changes in coronary luminal area of the normal vessel segments are shown in Fig. 2 and of the stenotic vessel segments in Fig. 3. *Normal coronary vessel segments* showed coronary vasodilation during exercise (±23%, $P < 0.01$) and after sublingual nitroglycerin (+40%, $P < 0.001$ vs rest) in the control group. Intracoronary administration of propranolol (group 2) was not associated with a significant change in coronary luminal area (+6%, NS) but during bicycle exercise there was coronary

dilation of the normal vessel segments (+13%, $P < 0.05$ vs rest) which further dilated after sublingual nitroglycerin (+31%, $P < 0.001$ vs rest). Intravenous administration of propranolol (group 3) was accompanied with a significant decrease in coronary luminal area of the normal vessel segment (−24%, $P < 0.001$), whereas bicycle exercise was associated with coronary vasodilation compared with the angiographic data after intravenous administration of propranolol, but remained more or less unchanged compared with the resting data (−2%, NS). After sublingual nitroglycerin there was coronary vasodilation of normal vessel segments (+21% $P < 0.01$ vs rest) in group 3.

Stenotic coronary vessel segments (Fig. 3) showed exercise-induced coronary vasoconstriction in the control group 1 (−29%, $P < 0.001$) which was prevented after intracoronary administration of propranolol (+22%, $P < 0.05$) in group 2. Sublingual nitroglycerin was accompanied in both group 1 (+12%, NS vs rest) and group 2 (+45%, $P < 0.01$) by coronary vasodilation. Intravenous administration of propranolol (group 3) was followed by coronary vasoconstriction of the stenotic vessel segments (−31%, $P < 0.001$). However, during submaximal exercise there was coronary vasodilation of the stenotic vessel segments compared with the data after intravenous propranolol, but there was no change in stenotic vessel segment (−3%, NS vs rest) compared with the data at rest. Administration of sublingual nitroglycerin in group 3 was accompanied by a significant increase in stenotic vessel area (+36%, $P < 0.001$ vs rest).

Discussion

The reduction in myocardial blood flow after intravenous administration of propranolol[1,2] has been attributed to a decrease in coronary luminal area[3], due to the unopposed alpha-adrenergic vasomotor tone after blockade of the beta-adrenergic receptors of the epicardial coronary arteries. Experimental data in the conscious dog[6] have shown, however, that the decrease in coronary cross-sectional area after intravenous administration of propranolol (beta-1 and beta-2 receptor blockade) or atenolol (selective beta-1 receptor blockade) is not prevented by alpha-adrenergic blockade with either phentolamine or prazosin. It was con-

cluded that the decrease in coronary cross-sectional area is probably related to the decrease in heart rate and contractility, but not due to the unopposed alpha-adrenergic tone. Since most patients with classic, exercise-induced angina pectoris respond well to betablocker treatment, the reduction in myocardial oxygen consumption during physical exercise cannot be explained by the occurrence of coronary vasoconstriction. It is a well-known fact that epicardial coronary arteries show vasodilation during dynamic exercise to meet the increased metabolic demands of the myocardium[4,5]. If intravenous administration of propranolol would cause coronary vasoconstriction during physical exercise, more patients with exercise-induced ischaemia would experience an adverse reaction to betablocker treatment.

The present study shows that intravenous administration of 0.1 mg kg^{-1} propranolol leads to a decrease in epicardial luminal vessel area of both normal and stenotic coronary arteries (Figs 2 and 3) which is not seen after intracoronary administration of 1 mg propranolol. Heart rate decreased significantly after intravenous administration of propranolol, whereas blood pressure decreased only slightly but not significantly. However, after intracoronary injection of propranolol, both heart rate and blood pressure remained unchanged. These differences in the haemodynamic determinants of myocardial oxygen consumption might explain the decrease in coronary luminal vessel area after intravenous propranolol, because it has to be assumed that not only heart rate but also contractility has decreased, which is another important determinant of myocardial oxygen consumption. However, it cannot be ruled out that the unopposed alpha-adrenergic vasomotor tone caused coronary vasoconstriction after intravenous administration of propranolol, as has been suggested by others[1,2] but which could not be confirmed in the conscious dog[6]. The fact that intracoronary administration of propranolol was not associated with coronary vasoconstriction supports the previous experimental data or Vatner and Hintze[6] which showed no direct effect of the betablockers on coronary vasomotion. It might be, however, that the drug had been washed out from the coronary vascular tree before it had blocked the beta-adrenergic receptors completely.

Dynamic exercise represents a physiological stimulus for coronary vasodilation to meet the metabolic demands of the myocardium during high energy expenditure such as bicycle exercise. In a previous report[4], we have shown that normal coronary arteries dilate during dynamic exercise, but eccentric coronary stenoses show exercise-induced coronary vasoconstriction. The exact mechanism of this exercise-induced stenosis narrowing is not clear but might be due to endothelial dysfunction (atherosclerotic alterations) with an insufficient production of the endothelium-derived relaxing factor[4,5] or due to a passive collapse of the free vessel wall within the stenosis during high flow states (Venturi mechanism) such as bicycle exercise[7]. Intracoronary administration of 1 mg propranolol prevented exercise-induced stenosis narrowing (Fig. 3), and after intracoronary pretreatment with propranolol there was coronary vasodilation ($+22\%$, $P < 0.05$) of the stenotic vessel segments during dynamic exercise. Intravenous administration of 0.1 mg kg^{-1} propranolol was associated with a decrease in luminal area of both normal and stenotic vessel segments (Figs 2 and 3) which was followed by an increase in coronary vessel area during bicycle exercise. At the maximal exercise level coronary luminal area reached its control value of both normal and stenotic coronary arteries. Sublingual administration of 1.6 mg nitroglycerin further dilated normal and stenotic vessel segments to a vessel area which was similar (NS) to the control group. Apparently, intravenous administration of propranolol is associated with a reduction in luminal vessel area of the epicardial coronary arteries, but the response of the coronary arteries to the dilator stimulus of bicycle exercise is not affected by the injection of propranolol prior to the exercise test. This observation parallels the clinical finding that most patients with exercise-induced angina pectoris do better after betablocker treatment because epicardial coronary arteries are still able to dilate during exercise, resulting in an increase in coronary blood flow.

The exact mode of action which prevents exercise-induced stenosis narrowing after intracoronary and intravenous administration of propranolol is not clear but might involve the following mechanisms:

1. The betablocking effect of propranolol

lessens the autoregulatory rise in coronary blood flow during exercise and lessens, therefore, the flow-dependent rise in transstenotic pressure gradient with a reduced flow-induced fall in stenosis distending pressure.

2. The rise in coronary vascular resistance after betablocker administration results in a higher poststenotic pressure and in a smaller transstenotic pressure gradient with a higher stenosis distending pressure.

3. The local anaesthetic effect of propranolol leads to a reduced influx of calcium into the smooth vascular musculature of the epicardial coronary arteries (calcium-antagonistic action) which is associated with coronary vasodilation during bicycle exercise. This mechanism, however, seems unlikely, since high blood levels of circulating propranolol are necessary for this local anaesthetic effect.

The possible role of these three mechanisms in coronary vasomotion during dynamic exercise cannot be estimated from our present data. However, our findings support the good clinical response to propranolol in most patients with classic, exercise-induced myocardial ischaemia.

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