Effect of Intravenous Propranolol on Coronary Vasomotion at Rest and During Dynamic Exercise in Patients With Coronary Artery Disease

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Coronary vasomotion was studied at rest and during bicycle exercise with biplane quantitative coronary arteriography in 28 patients with coronary artery disease. Patients were divided into two groups; the first 18 patients served as controls (group 1), and the next 10 patients were treated with propranolol 0.1 mg/kg, which was infused intravenously before exercise (group 2). Luminal area of a normal and a stenotic vessel segment was determined at rest, during supine bicycle exercise, and 5 minutes after sublingual administration of 1.6 mg nitroglycerin after exercise. In group 1, the normal vessel showed vasodilation (+16%, p<0.001) during exercise, whereas the stenotic vessel segment showed vasoconstriction (−31%, p<0.001). After sublingual administration of nitroglycerin, there was coronary vasodilation of both normal (36%, p<0.001 vs. rest) and stenotic (20%, p<0.001) vessel segments. Patients with angina pectoris during supine exercise (n=10) had significantly (p<0.05) more vasoconstriction (36%) than patients without angina (−23%). In group 2, intravenous administration of propranolol at rest was associated with a decrease in luminal area of both normal (−24%, p<0.001) and stenotic (−43%, p<0.001) vessel segments; however, during subsequent exercise, both normal (−2%, p=NS vs. rest) and stenotic (−3%, p=NS vs. rest) vessel segments dilated when compared with the measurements after propranolol. Administration of nitroglycerin further increased luminal area of both vessel segments (normal segment, +23%, p<0.001; stenotic segment, +46%, p<0.001 vs. rest). It is concluded that dynamic exercise in patients with coronary artery disease is associated with coronary vasodilation of the normal and vasoconstriction of the stenotic coronary arteries. Patients with exercise-induced angina had significantly more stenosis vasoconstriction than patients without angina although minimal luminal area at rest was similar. Intravenous administration of propranolol is accompanied by a significant decrease in coronary luminal area of both normal and stenotic vessel segments at rest, which is overridden by dynamic exercise and sublingual nitroglycerin. The reduction in myocardial oxygen consumption and the prevention of exercise-induced stenosis vasoconstriction might explain the beneficial effect of β-blocker treatment in most patients with coronary artery disease. (Circulation 1990;81:1225–1235)

β-Adrenergic receptor blockers are used extensively in the therapy of coronary artery disease. The beneficial effect of these agents has been attributed to a reduction of the imbalance between myocardial oxygen demand and supply, which alleviates myocardial ischemia.1–3 Exercise-induced angina pectoris has been explained by increased myocardial oxygen consumption in the presence of a fixed coronary artery stenosis.4 Vasoconstriction of stenotic coronary arteries has been reported during supine bicycle exercise, whereas normal coronary arteries showed vasodilation during exercise.5 It was postulated that exercise-induced stenosis narrowing was either because of active vasoconstriction6 or because of a passive collapse of a compliant wall segment (Venturi mechanism) within the stenosis.7,8 In patients with Prinzmetal angina pectoris, coronary spasm induced by exercise9,10 as well as exacerbation of coronary spasm after β-
blockade have been reported. These vasoconstrictive reactions contrast with the well-documented beneficial effect of β-blockers in patients with coronary artery disease. The purpose of the present study was to evaluate the effect of intravenous administration of propranolol on coronary vasomotion of normal and stenotic vessel segments in patients with coronary artery disease and classic exercise-induced angina pectoris.

**Methods**

**Patients**

In 28 men (mean age, 53 years; range, 37–67 years) with coronary artery disease and exercise-induced angina pectoris, biplane coronary arteriography was performed at rest and during supine bicycle exercise. Patients were selected on a consecutive basis when the following inclusion criteria were fulfilled: 1) a history of stable, effort-related angina pectoris (n = 26), ST segment depression equal to or more than 0.1 mV (range, 0.1–0.3 mV) (n = 23), or both during upright bicycle exercise; and 2) coronary artery stenosis clearly visible on angiography for quantitative evaluation. The first 18 patients with no medication before the exercise test served as controls (group 1); 12 of these 18 patients were included in a previous publication on coronary vasomotion in patients with coronary artery disease. The next 10 patients received propranolol 0.1 mg/kg i.v. before the exercise test (group 2). One-, two-, and three-vessel disease was present, respectively, in 44%, 28%, and 28% of group 1 patients and 40%, 40%, and 20% of patients in group 2 (all, p = NS). Ten patients in group 1 (55%) and seven patients in group 2 (70%, p = NS) had previous myocardial infarction. Left ventricular ejection fraction averaged 61±7% (range, 52–71%) in group 1 and 64±8% (range, 50–76%) in group 2. Because the most prominent and most severe stenosis was chosen for quantitative analysis, it is most likely that these vessels were the ones causing the patient’s ischemia during exercise.

All patients performed a precatheterization upright bicycle exercise test while on their usual medical regimen. In the control group, 12 patients were on β-blockers, 13 were on long-acting nitrates, and 11 were on calcium antagonists. In group 2, six patients were on β-blockers, eight were on long-acting nitrates, and seven were on calcium antagonists. All drugs were discontinued at least 24 hours before catheterization.

**Cardiac Catheterization**

Right and left heart catheterization by femoral approach were performed 1 hour after chlordiazepoxide 10 mg p.o. Diagnostic left ventriculography and biplane coronary arteriography using perpendicular views were performed with electrocardiographic, pulmonary artery, and aortic pressure monitoring. Coronary injections (5–7 ml at rest and 6–8 ml during exercise) of a nonionic contrast medium (iopamidol 755 mg/ml and trometamol 1 mg/ml [Iopamiro 370, Bracco, SA, Milano]) were filmed at 50 frames/sec. Twelve of the control patients were studied using ionic contrast medium (amidotrizoate [Urographin 76%, Schering AG, Zurich]).

**Study Protocol**

The present study followed the same exercise protocol as described previously. First, biplane left ventricular angiography was performed, followed by the diagnostic coronary arteriography. An interval of at least 10 minutes passed between the last diagnostic coronary arteriograms and the baseline coronary arteriogram for the exercise study. Aortic and pulmonary artery pressures were recorded immediately before coronary arteriography. Control biplane arteriography of the left coronary artery was carried out with the patient’s feet attached to the bicycle ergometer (model 380B, Siemens-Albis AG, Zurich). Exercise was begun at a level of 50–75 W and was increased every 2 minutes by 25–50 W. Repeat biplane coronary arteriography with concurrent aortic and pulmonary artery pressure recordings was performed at each 2 minutes and at the end of exercise. In the previously reported study, biplane coronary arteriography was carried out on patients at each minute during exercise; for the purpose of this study only the values at 2 minutes and at peak exercise were used. In group 2, propranolol 0.1 mg/kg i.v. was given during 5 minutes before the exercise test. Biplane coronary arteriography was repeated at 6, 9, and 12 minutes after initiation of the injection. Only the values 12 minutes after administration of propranolol are reported in Tables 1 and 2 and Figures 1 and 3–5. Then, exercise was begun using the same protocol as in the control group. Exercise was terminated because of anginal pain in 10 patients in group 1 and four patients in group 2 and because of fatigue in eight and six patients in groups 1 and 2, respectively. Mean duration was 3.6 minutes in group 1 and 3.8 minutes in group 2 (p = NS). Sublingual nitroglycerin (1.6 mg) was given immediately at the end of exercise, with coronary arteriography repeated 5 minutes, thereafter, when pain had already subsided. Exercise-induced angina pectoris (n = 14) was relieved by nitroglycerin in all cases within minutes. There were no complications related to the procedure in any of the 28 patients.

**Quantitative Coronary Arteriography**

Normal vessel segments as well as moderate- to severe coronary artery stenoses of the left coronary system were chosen for analysis (Figure 1). In each patient, a stenotic vessel was selected for study on the basis of clear visualization without overlapping vessels. A stenosis of the left anterior descending artery was analyzed in 10 patients in group 1 and seven patients in group 2, and a stenosis of the left circumflex artery was analyzed in eight patients of the control group and three patients of group 2. The
normal vessel segment was selected from a disease-free vessel when possible \((n=15)\); otherwise, an uninvolved prestenotic vessel segment \((n=3)\) was chosen at least four catheter-widths \((4\times2.5 \text{ mm}=10 \text{ mm})\) from the center of the stenosis, which was not used for quantitative evaluation. A normal vessel segment of the left anterior descending artery or its diagonal branch was analyzed in eight patients in group 1 and two in group 2, and a normal vessel segment of the left circumflex artery or its major branch was analyzed in 10 patients in group 1 and eight in group 2. In two patients, collaterals were observed from the right coronary artery to the left anterior descending coronary artery.

All coronary arteriograms were projected on a large screen at 2.5-fold magnification for quantitative analysis with a Vanguard Model XR 35 projector (Vanguard Corp., Melville, New York) or an Angiogram Projection System Model CAP-35B (Nishimoto Sangyo Corp., Tokyo).\(^5,16,17\) The outlines of coronary arteries were traced and digitized with an electronic digitizer (Numonics Corp., Montgomeryville, Pennsylvania) interfaced with a computer (PDP 11/34, DEC, Maynard, Massachusetts). A portion of the catheter of known dimension (near the tip) was traced for each cineframe and provided a scaling factor. Pincushion distortion was negligible for our system (Siemens Angioscope; Siemens-Albis AG); measurements at the periphery varied by less than 2% from measurements at the center.\(^5,16\) Therefore, a pincushion correction was not used in the present study.

The methodology for computerized analysis of coronary arteriograms was described previously.\(^5,16-18\) Briefly, a three-dimensional model of the vessel and stenotic segment was constructed by matching center lines of the individual biplane tracings and assuming the vessel cross section to be ellipsoidal. Then, the proximal and distal as well as the minimum cross-sectional areas of the vessel segment were calculated. The percentage of area stenosis was calculated from the minimal cross-sectional area of the stenosis divided by the average of the areas of the proximal and distal ends of the stenotic segment.

Quantitative evaluation was performed in a blinded fashion. The angiogram was projected, and the tracings were made by an observer unaware of the particular study conditions (i.e., control, propranolol, exercise, or sublingual nitroglycerin). For each vessel segment, six frames during middle to late diastole of one cardiac cycle were analyzed. When difficulties were encountered in visualization of the stenosis in one of the two biplane views because of overlying vessels or contrast reflux into the aorta, a monoplane view was used (three normal and 16 stenosed vessels). Similar data were reported by Brown and coworkers,\(^7\) who found that only 24% of all stenoses (vs. 43% in our study) were visualized sufficiently to use biplane analysis.

The effect of nonionic contrast mediums on coronary vasomotion was small, and variations in vessel diameter after iopamidol were less than 5% of the
control value. Because the type of contrast medium (ionic versus nonionic) could have affected coronary vasomotion because of its vasodilator capacity, patients in group 1 were subdivided into two groups, one receiving ionic contrast medium \((n=12)\) and the other receiving nonionic contrast medium \((n=6)\). These data have been summarized in Figure 2. There were no significant differences in coronary vasomotion between these two subgroups although normal vessel segment tended to dilate more during exercise with ionic than nonionic contrast material. Data are given at rest \(R\), after 2 minutes of exercise \(2\) min.\(EX\), and at end of peak exercise \(Max.\)\(EX\) as well as 5 minutes after 1.6 mg sublingual nitroglycerin \(NTG\) \(SL\).

**Figure 2.** Graphic plotting of effects of ionic \((amidotrizoate [Urographin 76%])\) and nonionic \((ipamidol 755 mg/ml \text{ and irometamol 1 mg/ml [Iopamiro 370]})\) contrast medium were evaluated on coronary vasomotion of normal \((cicles, solid line)\) and stenotic vessel segment \((triangles, dashed line)\) in 18 control patients \(group 1\). Twelve patients received ionic \(open symbols\) and six patients received nonionic \(closed symbols\) contrast medium. There were no significant differences in coronary vasomotion between these two subgroups although normal vessel segment tended to dilate more during exercise with ionic than nonionic contrast material. Data are given at rest \(R\), after 2 minutes of exercise \(2\) min.\(EX\), and at end of peak exercise \(Max.\)\(EX\) as well as 5 minutes after 1.6 mg sublingual nitroglycerin \(NTG\) \(SL\).

The increase in heart rate was significantly less \((p<0.05)\) at peak exercise in group 2 as compared with group 1. Mean aortic and pulmonary artery pressure increased significantly during exercise in groups 1 and 2 \((p<0.05)\). At peak exercise, the increase in mean pulmonary artery pressure was significantly less \((p<0.05)\) in group 2 when compared with the control group. After nitroglycerin, mean aortic and mean pulmonary artery pressure decreased in both groups.

### Results

**Exercise Data**

**Upright versus supine bicycle exercise.** Mean work load, the maximally achieved heart rate, and the rate-pressure product were significantly higher during the upright than during supine exercise test in both groups \((Table 1)\). In group 1, however, the age-, sex-, and height-corrected physical working capacity in percentage of the normal value was significantly lower during supine \((60\pm20\%)\) than during upright bicycle exercise \((86\pm20\%, p<0.001)\) but was not different between the two exercise tests in group 2 \((upright, 85\pm19\% \text{ vs. supine, } 77\pm14\%; NS)\).

**Control versus propranolol group (supine exercise).** Angina pectoris occurred in 10 of 18 patients in group 1 and four of 10 patients in group 2 \((p=NS)\). The rate-pressure product was slightly but not significantly lower during exercise in group 2 than in group 1. Because the work load was higher in group 2 \(because of the antiischemic action of propranolol\) than in group 1, a subset of the control group \(subset 1, n=10\) was selected to match the work load of group 2 \((Table 1)\). This subgroup showed a significantly higher rate-pressure product during exercise than group 2.

**Hemodynamic Data**

A representative case with coronary angiograms of a stenotic lesion at rest, after propranolol, and during supine bicycle exercise is shown in Figure 1. Normal coronary arteries showed an increase in mean luminal area during exercise \(+16\%, p<0.001\) in the control group \((Table 2)\). Administration of propranolol was associated with a decrease in mean luminal area of the normal vessel segment \(-24\%, p<0.001\). During supine bicycle exercise in group 2, the normal vessel segment reached its initial resting...
value during exercise (−2%, p=NS vs. rest). After nitroglycerin, the normal vessel segment dilated to a similar extent in both groups.

Intergroup comparisons showed that coronary luminal area at 2 minutes of exercise was significantly smaller in group 2 than in group 1. During peak exercise as well as after nitroglycerin, there were no significant differences between the two groups (Figure 5).

Stenotic coronary arteries showed in group 1 a decrease in minimal luminal vessel area during peak exercise (−31%, p<0.001), which was followed by an increase in stenotic vessel area after nitroglycerin (+20%, p<0.001 vs. rest) (Figure 4). In group 2, there was coronary stenosis narrowing 12 minutes after the administration of propranolol (−43%, p<0.001). Bicycle exercise was associated with an increase in stenotic vessel area as compared with the data after propranolol; however, minimal luminal area reached only its initial vessel area before the administration of propranolol (−3%, p=NS vs. rest). Administration of nitroglycerin was accompanied by an increase in minimal luminal area of the stenotic vessel segment (+46%, p<0.001 vs. rest), which was similar in the two groups (Figure 5).

Intergroup comparisons showed no significant difference in minimal luminal area at 2 minutes of exercise. During peak exercise, however, minimal luminal area was larger in group 2 than in the control group (p<0.001). After nitroglycerin, both groups showed coronary stenosis vasodilation to a similar extent (Figure 5).

**Table 1. Exercise Hemodynamic Data in Control Group 1 and Propranolol Group 2 as Well as Matched Control Subgroup 1 With Similar Work Load as in Group 2**

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<tr>
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<th>HR</th>
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<td>p (vs. R)</td>
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Given are mean values and standard deviation (SD) in the three groups.

HR, heart rate (beats/min); AP, peak systolic aortic pressure (mm Hg); RPP, rate-pressure product (mm Hg 10³/min); WL, work load (W); R, rest; PR, intravenous propranolol given before exercise test; EX, peak supine bicycle exercise; NTG, sublingual nitroglycerin given at end of exercise test.

*p<0.001, †p<0.05, ‡p<0.01.
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Coronary vasomotion
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endothelial dysfunction with insufficient production
of the endothelium-derived relaxing factor (EDRF),
because of platelet aggregation with release of the
vasoconstricting compound thromboxane A2, or
because of a passive collapse of the free vessel wall
when coronary flow velocity increases during exercise
(Venturi mechanism). Furthermore, a reduction
of coronary blood flow during exercise-induced tachy-
cardia in patients with severe coronary stenoses can,
by itself, attenuate stenosis narrowing by the absence of flow-induced vessel dilation. Which of these mechanisms is responsible for the observed phenomenon cannot be derived from the present analysis, but it seems obvious that exercise-induced stenosis narrowing can aggravate myocardial ischemia and represents, therefore, an important mechanism in the pathophysiology of angina pectoris.

ß-Blocking agents have been used frequently in the treatment of patients with coronary artery disease. The beneficial effects of these drugs have been attributed to the reduction of heart rate, blood pressure, and myocardial contractility, all of which reduce myocardial oxygen consumption at rest and during physical exercise. The reduction in myocardial blood flow after intravenous administration of propranolol has been associated with a decrease in coronary luminal area because of the unopposed ß-adrenergic receptor vasomotor tone after blockade of the ß-adrenergic receptors of the epicardial coronary arteries or because of a decrease in EDRF release when coronary blood flow is diminished. In dogs, the decrease in coronary cross-sectional area after intravenous administration of propranolol and atenolol, a selective ß₁-adrenergic receptor blocker, is not prevented by ß-adrenergic receptor blockade with either phentolamine or prazosin. Vatner and Hintze concluded that, under resting conditions, the decrease in coronary cross-sectional area after intravenous propranolol is probably related to the decrease in heart rate and contractility but not to an unopposed ß-adrenergic receptor tone. Brown and, more recently, Rafflenbeul and coworkers demonstrated, at rest, a decrease in coronary luminal area of both normal and stenotic coronary arteries after intravenous administration of propranolol in patients with coronary artery disease. In contrast, Gaglione and coworkers were not able to show coronary vasoconstriction after intracoronary administration of 1 mg propranolol. It is not clear whether there is significant first-pass binding after intracoronary injection of 1 mg propranolol; however, this small intracoronary dose of propranolol prevented exercise-induced stenosis vasoconstriction.

**Effect of Intravenous Propranolol on Coronary Vasomotion at Rest**

Administration of propranolol 0.1 mg/kg i.v. was associated with a significant decrease in luminal area of both normal and stenotic coronary arteries. This decrease was time dependent, and the maximum was
reached after an interval of 12 minutes (−11% and −21% after 6, −17% and −32% after 9, and −24% and −43% after 12 minutes in normal and stenotic coronary vessel segments, respectively). A similar time-dependent decrease in coronary luminal area was reported by Rafflenbeul and coworkers.30 Parallel to the decrease in coronary luminal area, there was a decrease in heart rate and, probably, myocardial contractility that was, however, not measured in the present study. Mean aortic pressure decreased only slightly but not significantly, whereas the rate-pressure product decreased significantly after intravenous propranolol. Thus, it is likely that myocardial oxygen consumption was reduced by intravenous administration of propranolol and that coronary blood flow decreased in parallel to this reduction in demand.20,22–30 It has been shown experimentally34–37 that a decrease in flow is followed by a decrease in coronary luminal area probably mediated by a reduction in EDRF release. The question arises whether the decrease in blood flow per se was responsible for the decrease in coronary luminal area or whether active vasoconstriction was induced by the unopposed α-adrenergic receptor vasmotor tone. This question cannot be answered definitively by the present analysis because coronary blood flow was not measured.

Effect of Intravenous Propranolol on Coronary Vasomotion During Dynamic Exercise

Dynamic exercise represents a physiological stimulus for coronary arteries to dilate and to meet the metabolic demands of the myocardium during high-energy expenditure such as bicycle exercise. Coronary blood flow is known to decrease after intravenous β-blockade not only at rest but also during exercise.38 It has been shown experimentally, however, that subendocardial blood flow is augmented during exercise-induced ischemia after intravenous administration of atenolol.38 In fact, the endocardial-epicardial perfusion ratio increased after β-blockade in the ischemic region during exercise because of a slight decrease (p=NS) in subepicardial blood flow and a slight increase (p=NS) in subendocardial blood flow.38 Mean normalized myocardial blood
flow increased in the ischemic region after atenolol, which indirectly supports our findings in patients with coronary artery disease, that is, that minimal luminal area is larger during exercise after intravenous administration of propranolol than during exercise without the drug. With the assumption of an increase in coronary blood flow consequent to the longer diastolic time intervals during exercise, a reduction of coronary vessel narrowing could be explained by an increase in EDRF release. This vasodilator mechanism might have overridden the passive vessel collapse, which might have been operative with an increase in transstenotic flow velocity. If blood flow increases or does not decrease during exercise after regional β-blockade, the passive collapse at the site of the stenosis might have been prevented, especially when there was an increase in distal coronary pressure after propranolol-induced peripheral coronary vasoconstriction. A third possible although unlikely mechanism for preventing exercise-induced stenosis narrowing involves the local anesthetic effect of propranolol, which has been shown experimentally to reduce calcium influx into the smooth vasculature (calcium antagonistic action) and to induce coronary vasodilation. The concentration required for this calcium antagonistic effect, however, has been shown to be much higher (>10,000 ng/ml) than the concentration therapeutically used (<100 ng/ml). 39

Relation Between Angina Pectoris, Stenosis Severity, and Coronary Vasomotion

The occurrence of angina pectoris during exercise is usually preceded by hemodynamic alterations of systolic and diastolic function with an increase in left ventricular end-diastolic pressure and ST changes in the electrocardiogram. Thus, patients have been divided into subgroups of patients with and without angina pectoris to evaluate the effect of coronary vasomotion on myocardial ischemia and the clinical symptoms. Ten of the 18 patients in the control group and four of the 10 patients in group 2 had angina pectoris during supine bicycle exercise. When the hemodynamic and angiographic data of these subgroups were analyzed, it became evident that, only in the control group (Table 3), was myocardial ischemia more severe in patients with exercise-induced angina (no increase in mean aortic pressure but significant increase in mean pulmonary artery pressure) than in patients without exercise-induced angina. Parallel to the hemodynamic changes, the stenotic vessel segment showed significantly (p<0.05) more exercise-induced vasoconstriction in patients with angina pectoris (−36%) than without angina pectoris (−23%). These differences were not evident after pretreatment with intravenous propranolol, and thus, these data are not reported. Despite the fact that exercise-induced vasoconstriction was more pronounced in patients with than without angina, minimal luminal area at rest was not different in these two subgroups, indicating that a passive collapse (Venturi mechanism) is unlikely to have contributed to this phenomenon. It is possible, however, that stenosis morphology was different between these patients and that endothelial dysfunction was more pronounced, or turbulent coronary blood flow caused platelet aggregation with release of thromboxane A2 and serotonin in patients with exercise-induced angina. The work load was also significantly lower in patients who experienced angina pectoris during exercise. Consecutively, the rate-pressure product and, thus, myocardial oxygen con-

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<th>Table 3. Hemodynamic and Angiographic Data in Patients With and Without Exercise-Induced Angina Pectoris</th>
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Given are mean values and standard deviation (SD) in two subgroups. Values in parentheses are millimeters squared. Patients with angina show significantly more stenosis vasoconstriction during exercise than patients without angina. Hemodynamic data indicate more severe ischemia in these patients despite lower work load during exercise. HR, heart rate (beats/min); MAP, mean aortic pressure (mm Hg); RPP, rate-pressure product; MPAP, mean pulmonary artery pressure (mm Hg); WL, work load; R, rest; EX, peak supine bicycle exercise; NTG, sublingual nitroglycerin given at end of exercise test; N, normal vessel; S, stenotic vessel.

*p<0.001, tp<0.05, tp<0.01.
sption was lower in these patients than in the others. The correlation between stenosis severity (minimal luminal area) and exercise-induced changes in minimal luminal area was weak (group 1 correlation coefficient \( r = 0.42; p < 0.05; y = -0.40 + 0.14x \) and was shifted upward after propranolol (group 2, \( r = 0.39; p = NS; y = 0.64 + 0.11x \)), suggesting that factors other than stenosis severity alone, such as circulating hormones, nervous regulation, and endothelial substances (e.g., EDRF, endothelin, and neuropeptides), are responsible for exercise-induced stenosis narrowing. Apparently, exercise-induced vasoconstriction aggravates myocardial ischemia during exercise, and it seems that angina pectoris occurs at a much lower work load in these patients than in those without angina despite the same resting luminal area.

**Limitations of the Study**

The effect of the ionic and nonionic contrast medium was evaluated in the present analysis (Figure 2) by comparing the data of patients receiving amidotrizoate (\( n = 12 \)) or iopamidol (\( n = 6 \)). There were, however, no significant differences in coronary vaso-motion of the normal and stenotic vessel segment; however, exercise-induced vasodilation of the normal segments tended to be more pronounced after injection of the ionic than after injection of the nonionic contrast material. This tendency was not seen for the stenotic vessel segment. Thus, our data on exercise-induced coronary vasoconstriction are not influenced by the use of ionic or nonionic contrast material and can be interpreted as being representative.

Coronary blood flow was not measured in the present study for several reasons. First, the study protocol was complicated, and a longer catheterization time and a more complex instrumentation would have increased the risk for the patient. Second, methods for measuring coronary blood flow under exercise conditions in humans are problematic. Doppler flow probes measure flow velocity in individual coronary arteries but might have caused vessel dissection during exercise, and their accuracy with catheter movement during exercise is difficult to evaluate. Parametric digital angiography has been used for measuring relative coronary blood flow under resting conditions and after pharmacologically induced vasodilatation; however, motion artifacts from respiratory movement under exercise conditions can influence these measurements adversely, and transmural blood flow cannot be measured by this method. Coronary sinus thermodilution techniques do not allow the assessment of regional coronary blood flow, which is especially important in patients with coronary artery disease.

The accuracy of quantitative coronary arteriography has been well established in our laboratory\(^5,16,17\) and by the extensive validation studies of Brown and coworkers\(^41\) and Gould and coworkers.\(^42\) Brown and coworkers\(^41\) reported that the accuracy of quantitative coronary arteriography is within 0.08 mm for measurements of known dimensions and 0.10 mm for minimum diameter estimates. The changes observed in our study, such as the 0.4 mm\(^2\) (0.20-mm diameter) decrease in the stenosis area at peak exercise in the control group, are small but clearly larger than the reported angiographic resolution. In the present study, a monoplane angiographic assessment was used in 57\% of all stenoses because of overlying vessels or contrast reflux into the aorta; however, the correlation between monoplane and biplane coronary luminal area assessment has been evaluated previously in our laboratory\(^5,16,17\) and was excellent \((n = 22, r = 0.979)\). Therefore, the observed relative changes after several interventions can be considered representative even with monoplane assessment.

**References**

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