

Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin

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ABSTRACT To study the vasomotility of normal and diseased coronary arteries during dynamic exercise, symptom-limited supine bicycle exercise during cardiac catheterization was performed by 18 patients with classic angina pectoris. The cardiovascular response was assessed by hemodynamic measurements and computer-assisted determination of normal and stenotic coronary artery luminal areas from biplane coronary angiograms made before, during, and after exercise. After baseline measurements were recorded, 12 patients (group 1) performed bicycle exercise for 3.4 min (mean), reaching a maximum workload of 81 W (mean); at the end of exercise they received 1.6 mg sublingual nitroglycerin. After measurements at rest in six other patients (group 2), 0.1 mg intracoronary nitroglycerin was given, followed by exercise (3.8 min, 96 W; NS) and sublingual nitroglycerin as in group 1. During exercise in group 1, luminal area of the coronary stenosis decreased to 71% of resting levels ($p < .001$), while area of the normal coronary artery increased to 123% of control ($p < .001$). After sublingual nitroglycerin at the end of exercise, area of the normal vessel further increased to 140% of control ($p < .001$), while luminal area of the stenosis dilated to 112% of resting levels ($p < .001$ vs exercise, NS vs rest). Pretreatment with intracoronary nitroglycerin increased both normal (121%; $p < .05$) and stenotic (122%; $p < .05$) luminal areas, while preventing the previously observed narrowing of stenosis during exercise (114%; NS). Exercise resulted in a similar heart rate-systolic pressure product and caused angina pectoris in two-thirds of the patients in each group. However, patients pretreated with intracoronary nitroglycerin (group 2) had a lower mean pulmonary arterial pressure during maximum exercise (35 mm Hg) than those patients (group 1) not receiving pretreatment (47 mm Hg; $p < .001$). Group 2 patients reached a percentage of their predicted work capacity (65%) that was about the same as that during previous upright bicycle exercise (71%; NS), while group 1 patients had a significantly lower work capacity (51% of predicted) than that before catheterization (82%; $p < .001$). Hence, narrowing of coronary artery stenosis during dynamic exercise is attributable to active vasoconstriction due to its reversibility by preexercise intracoronary nitroglycerin. Patients who did not experience narrowing of stenosis during exercise (group 2) had less evidence of myocardial ischemia (lower mean pulmonary arterial pressure) and maintained their work capacity. This indicates that vasoconstriction of coronary artery stenosis can be an important mechanism in causing myocardial ischemia during dynamic exercise in patients with classic angina pectoris.

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CORONARY ARTERY STENOSIS is being viewed to an increasing extent as a dynamic element in the induction of myocardial ischemia.¹ The occurrence of spasm at the site of coronary artery disease has been

well documented at rest^{2,3} and during exercise⁴⁻⁶ in patients with Prinzmetal's angina pectoris accompanied by ST segment elevation. In contrast, classic angina pectoris has been presumed to be caused by an increase in myocardial oxygen demand relative to a coronary blood supply limited by a fixed stenosis.⁷

The ability of a coronary stenosis to change in size is predicated on the presence of an intact musculoelastic wall segment within the stenosis. Autopsy series have documented compliant tissue arcs of at least 30 degrees in over 70% of stenoses of greater than 50% severity.^{8,9} Brown et al.¹⁰ have suggested that active vaso-

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constriction and passive collapse of the free vessel wall contribute to a decrease in cross-sectional area of a stenosis and an increase in coronary large vessel resistance and thus a limitation of coronary blood flow. This would be particularly evident at times of high flow rates, such as during dynamic exercise.

The purpose of this study was to determine the reaction of stenotic and normal coronary arteries to dynamic exercise in patients with the classic syndrome of purely exertional angina associated with ST segment depression.

Methods

Study population. Ten patients with coronary artery disease were studied for the assessment of interobserver variability of the computer-aided system for quantitative analysis of coronary artery stenoses. This group was made up of 10 consecutive patients undergoing diagnostic cardiac catheterization with biplane coronary angiography.

Exercise coronary angiography was performed in 18 men with coronary artery disease, one with single-vessel, three with two-vessel, and 14 with three-vessel disease. The first 12 patients constituted group 1, and the next six patients, in which exercise was preceded by administration of intracoronary nitroglycerin, constituted group 2. All patients performed a precatheterization upright bicycle stress test while on their long-term medical regimen. The patients were selected on a consecutive basis when the following inclusion criteria were fulfilled: (1) a history of stable exertional angina pectoris or signs of exercise-induced myocardial ischemia during a precatheterization exercise test, and (2) coronary artery stenosis visible during cardiac catheterization for quantitative assessment. There was no randomization to treatment.

The mean age of the patients was 53 years (range 36 to 67). Ten of the 18 patients had a history of myocardial infarction. No patient had a history of unstable angina or of ST segment elevation during dynamic exercise. There was no significant difference between groups with respect to long-term medical therapy: 12 of 12 patients in group 1 and five of six patients in group 2 were receiving a β -receptor blocker, eight of 12 and five of six took a nitrate preparation, and five of 12 and three of six were on a calcium antagonist. Informed consent was obtained from all patients.

Cardiac catheterization. Patients underwent right and left heart catheterization while in the fasting state. Premedication consisted of 10 mg chlordiazepoxide administered orally 1 hr before catheterization. All drugs were discontinued at least 12 hr before the study.

Aortic pressure was measured with a Judkins catheter introduced through the right femoral artery. Pulmonary arterial pressure was measured with a No. 7F pacing catheter with a side lumen for pressure recordings introduced through the right femoral vein. A standard lead of the routine electrocardiogram (ECG) was monitored in all patients at rest and during exercise. Aortic and pulmonary pressure, cinemarkers for the right anterior oblique (RAO) and left anterior oblique (LAO) projections, and the ECG were recorded at a paper speed of 250 mm/sec (Electronics for Medicine, model VR12) in patients at rest and during exercise coronary angiography. Simultaneous biplane coronary angiograms were obtained in the 30 degree RAO and 60 degree LAO projections at a filming rate of 50 frames/sec.

Study protocol. First, routine left ventricular biplane angiography was performed, then biplane coronary angio-

graphic examination of the right and left coronary arteries was carried out for diagnostic purposes. Subsequently, the patient's feet were secured to a bicycle ergometer (Siemens-Elema AG, model 380B). Aortic and pulmonary arterial pressures were recorded while a baseline biplane left coronary angiogram was obtained. An interval of at least 10 min passed between the time the last diagnostic coronary angiogram was obtained and this baseline angiogram was obtained for the exercise study. Exercise was then begun by the first 12 patients (group 1) at 50 to 75 W and workload was increased every 2 min in increments of 25 to 50 W. Repeat biplane coronary angiographic examination with concurrent aortic and pulmonary arterial pressure recordings was performed each minute and at the end of exercise (figure 1). Intracatheterization exercise was terminated because of anginal pain, fatigue, or greater than 0.2 mV ST segment depression on the ECG. Nitroglycerin, 1.6 mg sublingually, was given immediately at the end of exercise, and coronary arteriographic examinations were repeated at 2 to 3 min and at 4 to 6 min thereafter, when the pain had already subsided.

Six patients (group 2) were studied with a similar protocol with one difference: after the baseline angiogram was obtained, 0.1 mg nitroglycerin was injected into the left coronary artery over 30 sec. Two minutes after the intracoronary injection of nitroglycerin, another biplane angiogram was obtained, and then bicycle exercise proceeded as described above. After each minute of exercise a coronary arteriogram was obtained. On completion of the exercise study, 1.6 mg sublingual nitroglycerin was administered and biplane coronary angiograms were again obtained at 2 to 3 and 4 to 6 min. The exercise-induced angina pectoris was relieved within minutes by sublingual nitroglycerin in all cases. There were no complications related to the procedure in any of the 28 patients.

Quantitative coronary angiography. Moderate-to-severe coronary artery stenoses and segments of normal vessels of the left coronary system were chosen for analysis (figures 1 and 2). In each patient a stenosis was selected for quantitative analysis that could be easily identified with no superposition of other vessels or structures. A stenosis of the left anterior descending artery was analyzed in six group 1 and two group 2 patients, and one of the left circumflex artery was analyzed in six group 1 and four group 2 patients. The normal vessel segment was selected from a disease-free vessel when possible ($n = 8$); otherwise an uninvolved prestenotic vessel segment ($n = 10$) was chosen. In five patients this uninvolved prestenotic segment included a side branch of the stenotic vessel (two diagonal, one posterolateral, and two intermediate branches) and in the other five patients the normal vessel segment chosen was at least four catheter widths ($4 \times 2.5 \text{ mm} = 10 \text{ mm}$) from the center of the stenosis. A normal vessel segment of the left anterior descending artery or of one of its major branches was analyzed in six group 1 and one group 2 patients, and was of the left circumflex artery or one of its major branches in five group 1 and five group 2 patients. The segment was of the left main coronary artery in one group 1 patient. No direct evidence was obtained by left ventricular angiocardiology that the vessels selected for quantitative assessment were the ones causing the patients' ischemia during exercise. However, the most prominent and most severe stenosis was chosen for quantitative analysis to obtain meaningful data with regard to exercise-induced myocardial ischemia. In only two patients were collaterals observed from the right coronary artery to the left anterior descending coronary artery that was subsequently selected for quantitative analysis.

The angiographic films were projected (Vanguard Instrument Corp., model XR35) on a screen to a size approximately 2.5 times normal. Tracings were then made from the simultaneous LAO and RAO frames that best visualized the stenosis or normal vessel segment. All analysis of vessel segments was per-

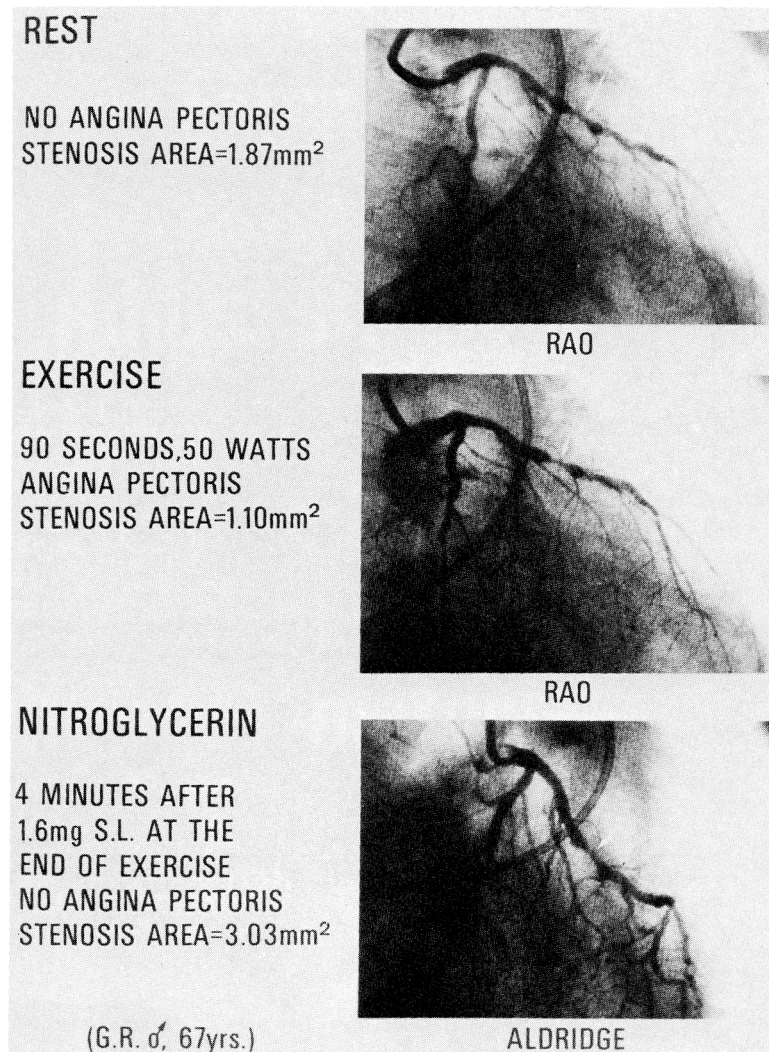


FIGURE 1. Angiograms showing exercise-induced narrowing of a stenosis of the left anterior descending coronary artery (arrow) in a 56-year-old man (patient 7) with a history of exertional angina with ST segment depression. This narrowing from 1.3 mm² at rest (*top*) to 1.0 mm² at peak exercise (*middle*) was associated with angina pectoris and an increase in mean pulmonary arterial pressure from 30 to 52 mm Hg (table 2). After sublingual nitroglycerin given at the end of exercise, the area of stenosis returned to 1.3 mm² (*bottom*), angina resolved, and mean pulmonary arterial pressure decreased to 28 mm Hg.

formed 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, exercise, or nitroglycerin. Tracings of stenoses included angiographically normal vessels both proximally and distally. For a given patient, the angiograms were traced at the same time in the cardiac cycle. A section of the catheter of known dimensions was traced as a scaling factor.¹¹ By filming a grid at the conclusion of each study, pincushion distortion was found to be small for our system; measurements made at the periphery varied by less than 2% from those made at the center. Therefore, a correction was not used. The stenoses were then traced on a digitizer (Numonics Corp.) linked to a PDP 11/34 computer.

The computer program for quantitative analysis of coronary artery stenosis has been described elsewhere.¹¹ A three-dimensional model of the vessel segment was constructed from the biplane tracings. The proximal and distal as well as minimal cross-sectional areas of the vessel segment were calculated by the computer. Area of the normal vessel was calculated as the average of the proximal and distal measurements. Percent 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. For each vessel segment, three frames were analyzed and the results were expressed as the mean. On average, the standard deviation of this

mean value for the cross-sectional area of each stenosis and normal segment was 6.0%.

When difficulties were encountered in visualization of the stenosis in one of the biplane views due to overlying vessels or contrast reflux into the aorta, a single view was used ($n = 1$ for normal and $n = 11$ for stenotic vessels). In these cases, the computer constructed a circular lumen to calculate the cross-sectional area. These findings are comparable to the data reported by Brown et al.,¹² who found that 24% of all stenoses (vs seven of 18 or 39% in our study) were visualized sufficiently to use biplane analysis.

To establish interobserver variability, vessel segments in 10 consecutive patients undergoing diagnostic biplane coronary angiography were analyzed independently by two observers. The standard error of the estimate for 22 measurements of luminal area in the 10 patients was 0.39 mm² (9.3% of the mean vessel area) for monoplane (correlation coefficient .992) and 0.30 mm² (7.9% of the mean vessel area) for biplane analysis (correlation coefficient .991). Comparison of monoplane and biplane data showed a good correlation coefficient for both observers (.979 and .978, respectively), with a standard error of the estimate of 0.473 mm² for observer 1 (12.3% of the mean biplane vessel area) and 0.475 mm² for observer 2 (12.5% of the mean biplane vessel area). Although the correlation between monoplane and biplane data was excellent, the standard error of

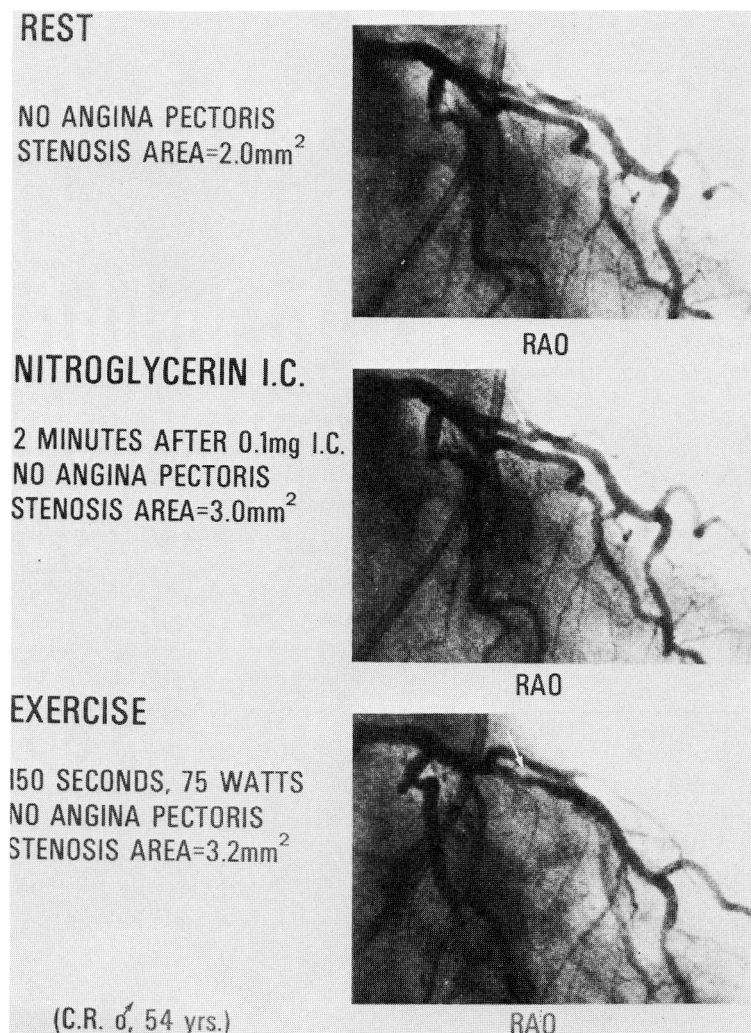


FIGURE 2. Angiograms showing results of injection of nitroglycerin (0.1 mg) into the left coronary artery of a 54-year-old man (patient 15). Luminal area of stenosis (arrow) increased from 2.0 mm² (top) to 3.0 mm² (middle), without significant hemodynamic effects (table 2). During subsequent supine bicycle exercise, area of stenosis remained dilated (bottom), while mean pulmonary arterial pressure rose from 19 to 29 mm Hg with no angina pectoris.

the estimate was larger than that for biplane data alone because of the eccentric location of most coronary artery stenoses.

Statistical analysis. The hemodynamic and arterial cross-sectional area response to exercise and nitroglycerin, expressed in absolute values and in percent of control, were compared by two-way analysis of variance for repeated measures. When a comparison was made with the results of the precatheterization upright bicycle exercise test, a paired *t* test was used. Comparisons between responses in groups 1 and 2 were made by Wilcoxon rank-sum test. In tables and figures the mean \pm 1 SD is reported, unless otherwise indicated.

Results

Clinical data. There was no significant difference between patients in groups 1 and 2 with respect to age (53 vs 54 years) or New York Heart Association classification (mean 1.9 vs 2.5). There was a statistically insignificant tendency toward more frequent previous myocardial infarction in group 1 (eight of 12 patients) than in group 2 (two of six). Ejection fraction was normal in group 1 (61%) and in group 2 patients (58%; NS).

Exercise capacity. The responses to the baseline upright bicycle as well as to the intracatheterization su-

pine bicycle exercise tests are listed in table 1. Despite achieving similar absolute workloads (81 vs 96 W; NS), group 1 patients actually reached a significantly lower percentage of their predicted work capacity (in watts) during the supine bicycle stress test in the catheterization laboratory (51%) than during the prior upright test (82%; *p* < .001). In contrast, group 2 patients achieved similar workloads when expressed as a percentage of their predicted capacity (upright, 71%; supine, 65%; NS).

Groups 1 and 2 achieved similar heart rates (99 vs 95 beats/min) and duration of exercise (3.4 vs 3.8 min). The maximal level of exercise reached, as measured by the heart rate-systolic blood pressure product, was little different in group 1 (14,500 mm Hg/min) and group 2 (13,200 mm Hg/min). During intracatheterization supine bicycle exercise, both group 1 and 2 patients had similar, significantly lower rate-pressure products compared with during the earlier upright bicycle test (76% of upright, *p* < .005; 68% of upright, *p*

TABLE 1

Results of baseline upright and intracatheterization supine bicycle exercise tests

Patient No.	Upright bicycle exercise							Supine bicycle exercise					
	WL	%	HR	BP	RPP	ST	T	WL	%	HR	BP	RPP	T
Group 1													
1	135	104	105	155/75	163	0.3	A	75	56	87	188/108	164	A
2	160	99	116	130/70	151	0.2	A	50	31	76	126/72	96	A
3	110	73	126	115/70	145	0.1	A	50	33	101	101/63	102	A
4	80	50	135	145/75	196	0.2	A	50	31	102	141/74	144	A
5	110	81	140	180/90	252	0.1	A	50	37	99	167/85	165	A
6	150	97	150	220/105	330	0.1	F	75	48	85	171/89	145	F
7	70	49	109	120/60	131	0.2	A	50	35	103	96/63	99	A
8	200	100	113	165/75	186	0.3	A	150	75	114	158/90	180	A
9	160	102	108	180/80	194	0	F	125	80	108	178/76	192	A
10	120	77	143	185/85	265	0.2	F	100	65	104	137/68	142	F
11	120	77	134	175/70	235	0.1	F	100	64	105	152/76	160	F
12	130	77	108	145/60	157	0.1	F	100	60	99	154/86	152	F
Mean	129	82	124	160/76	200	0.15	7/12	81 ^D	51 ^D	99 ^C	147/79	145 ^B	8/12
± SD	36	19	5	31/13	59	0.1		34	18	11	29/13	31	
Group 2													
13	130	76	128	140/85	179	0	A	100	59	72	107/72	77	A
14	70	50	98	120/75	118	0.2	A	100	71	101	87/49	88	S
15	90	72	105	200/90	210	0.3	A	75	60	70	156/73	109	F
16	150	101	168	155/70	260	0.2	F	125	84	126	172/83	217	A
17	80	50	126	165/90	208	0.3	A	100	63	113	145/83	164	A
18	110	76	115	160/75	184	0.3	A	75	52	86	162/78	139	A
Mean	105	71	123	157/80	193	0.2	5/6	96	65	95 ^A	138/73	132 ^B	4/6
± SD	31	19	10	27/10	47	0.1		19	11	23	34/13	53	

WL = workload at maximal exercise (W); % = workload as a percent of predicted work capacity; HR = heart rate (bpm); BP = blood pressure (mm Hg); RPP = heart rate–systolic blood pressure product (mm Hg/min); ST = ST segment depression (mV) during upright bicycle exercise; T = reason for termination of exercise test; A = angina pectoris; F = fatigue; S = ST depression of greater than 0.2 mV.

Significance of supine bicycle exercise when compared with upright bicycle exercise: ^Ap < .05; ^Bp < .01; ^Cp < .005; ^Dp < .001.

< .005, respectively). Intracatheterization exercise was discontinued due to angina, fatigue, or greater than 0.2 mV ST segment depression in eight, four, and no group 1 patients, and four, one, and one group 2 patients, respectively.

Hemodynamic data. As shown in table 2, the heart rate and the mean aortic and pulmonary arterial pressures did not change significantly after intracoronary nitroglycerin, but increased during exercise and decreased toward resting levels after exercise and the administration of sublingual nitroglycerin. The only significant difference between groups in the absolute values of these parameters was in the level of mean pulmonary arterial pressure during exercise: 47 mm Hg in group 1 vs 33 mm Hg in group 2 ($p < .005$). There was a significant difference between groups in the increase in mean aortic pressure achieved during exercise (from 87 to 107 mm Hg in group 1 [$p < .001$] vs from 92 to 99 mm Hg in group 2 [NS]).

Quantitative coronary angiography. The responses of normal and stenotic coronary artery segments to dy-

namic exercise followed by sublingual nitroglycerin without (group 1) and with (group 2) preexercise intracoronary nitroglycerin are summarized in table 3 and figures 3 and 4. Figure 5 shows the data on cross-sectional areas of normal and stenotic vessels presented in table 3 in terms of percent of resting values; the results will henceforth be discussed in these terms. In group 1, exercise induced a significant increase in cross-sectional area of normal vessels to 123% of control ($p < .01$). There was no difference in the response of a normal vessel segment to exercise whether it was in the same vessel as the stenosis (130% increase) or in the contralateral vessel (119% increase; NS). After sublingual nitroglycerin, this vasodilation was further augmented to 140% of control ($p < .001$ vs control; NS vs peak exercise). In the stenotic segments during exercise, in group 1 patients there was a marked decline in luminal area of the stenosis to 71% of control ($p < .001$), with an increase to 112% of control levels after sublingual nitroglycerin at the end of exercise (NS vs control; $p < .001$ vs exercise).

TABLE 2
Hemodynamic response to supine bicycle exercise and nitroglycerin

Patient No.	Heart rate (bpm)				Mean aortic pressure (mm Hg)				Mean pulmonary arterial pressure (mm Hg)			
	R	NC	EX	NL	R	NC	EX	NL	R	NC	EX	NL
Group 1												
1	60		87 ^A	68	106		141 ^A	114	25		49 ^A	26
2	48		76 ^A	62	95		94 ^A	95	27		40 ^A	29
3	69		101 ^A	65	65		79 ^A	62	17		35 ^A	10
4	62		102 ^A		71		101 ^A					
5	60		99 ^A	70	96		119 ^A	103	32		58 ^A	41
6	50		85	49	105		123					
7	69		103 ^A	74	61		77 ^A	73	30		52 ^A	28
8	48		114 ^A	63	75		119 ^A	81	18		48 ^A	20
9	62		108 ^A	84	104		118 ^A	102	26		50 ^A	15
10	60		104	85	80		96	62	25		44	22
11	75		105	84	100		107	66	31		45	23
12	49		99	62	89		114	67	28		50	22
Mean	59		99 ^C	70 ^B	87		107 ^C	83	26		47 ^C	24
±SD	9		11	12	16		19	19	5		6	8
Group 2												
13	68	67	72 ^A	63	81	93	86 ^A	68	22	24	22 ^A	16
14	69	74	101	79	82	96	65	88	23	25	32	25
15	50	50	70	52	96	104	103	104	20	19	29	19
16	93	82	126 ^A	83	89	93	120 ^A	90	29	15	41 ^A	27
17	66	74	113 ^A	69	86	95	108 ^A	86	25	21	36 ^A	16
18	71	58	86 ^A	66	115	105	112 ^A	87	29	23	42 ^A	18
Mean	70	68	95 ^B	69	92	98	99	87	25	21	35 ^{B,D}	20
±SD	14	12	23	11	13	5	20	11	4	4	8	5

These values correspond to the measurements of cross-sectional luminal area of coronary stenoses and normal vessels presented in table 3.

R = rest; NC = intracoronary nitroglycerin; EX = peak supine bicycle exercise; NL = sublingual nitroglycerin given at the end of exercise.

^AAngina pectoris.

Significance vs resting values: ^Bp < .005; ^Cp < .001.

Significance vs group 1: ^Dp < .005.

In group 2 patients, vasodilation of the normal segments occurred after 0.1 mg intracoronary nitroglycerin (121%; p < .05) and persisted during maximum exercise (129%; p < .01) and after sublingual nitroglycerin administered at the end of exercise (123%; p < .01) (figure 5). In the stenotic segments, preexercise intracoronary nitroglycerin caused a mean increase to 122% of control (p < .05), with four of six stenoses increasing by more than 10% (table 3). The dilation persisted during the first 2 min of exercise (123%; p < .05), but decreased slightly toward resting levels at peak exercise (114%; NS).

Percent stenosis in group 1 patients was 59 ± 14% at rest, vs 68 ± 15% (p < .01 vs rest) at peak exercise and 57 ± 17% following sublingual nitroglycerin after exercise. In group 2 patients, percent stenosis changed little during the study: from 58 ± 19% at rest, to 61 ± 19% after intracoronary nitroglycerin, to 64 ± 14%

during peak exercise, and to 61 ± 20% after sublingual nitroglycerin.

Discussion

Narrowing of coronary artery stenosis in response to dynamic exercise represents a significant element in the pathogenesis of myocardial ischemia. Brown et al.¹⁰ found that the luminal areas of normal coronary arteries and coronary stenoses decreased by 14% and 35%, respectively, during isometric handgrip exercise. In contrast, a second handgrip test during intracoronary infusion of nitroglycerin showed a 32% increase in cross-sectional area of the stenosis. Despite a similar increase in the heart rate–systolic pressure product, intracoronary nitroglycerin during handgrip exercise caused no increase in pulmonary capillary wedge pressure, whereas handgrip alone caused narrowing of stenosis with a 56% increase in capillary

TABLE 3

Luminal area of normal and stenotic coronary arterial segments in response to dynamic exercise and nitroglycerin

Patient No.	Normal vessel (mm ²)				Stenotic segment (mm ²)			
	R	NC	EX	NL	R	NC	EX	NL
Group 1								
1	2.2		2.7 ^A	3.1	2.3		1.1 ^A	2.3
2	4.4		5.3 ^A	5.1	1.0		0.7 ^A	0.9
3	2.0		4.0 ^A	3.8	4.6		3.6 ^A	5.4
4	2.7		3.0 ^A		1.4		0.8 ^A	
5	1.9		2.0 ^A	2.9	1.9		1.1 ^A	3.0
6	2.6		2.6		1.5		1.4	
7	3.2		4.4 ^A	4.5	1.3		1.0 ^A	1.3
8	4.2		4.4 ^A	4.9	2.1		1.2 ^A	2.2
9	17.0		16.8 ^A	20.0	1.9		1.5 ^A	1.8
10	4.3		5.4	7.3	1.7		1.3	2.5
11	4.3		4.7	5.1	3.2		2.6	3.3
12	7.0		8.8	9.3	2.1		1.8	2.1
Mean	4.7		5.3 ^B	6.6 ^{D,E}	2.1		1.5 ^C	2.5 ^F
±SD	4.1		4.0	5.1	1.0		0.8	1.3
Group 2								
13	9.7	11.0	10.6 ^A	10.7	3.7	3.6	3.2 ^A	2.7
14	2.0	2.4	2.3	2.0	2.4	2.7	2.3	2.8
15	4.6	6.1	7.4	6.3	2.0	3.0	3.2	2.2
16	5.9	7.3	7.4 ^A	7.1	0.9	1.2	1.1 ^A	1.1
17	4.9	5.2	6.9 ^A	5.9	2.1	2.3	2.5 ^A	3.0
18	6.0	7.8	7.2 ^A	8.8	4.5	5.9	4.6 ^A	5.6
Mean	5.5	6.6 ^B	7.0 ^C	6.8 ^B	2.6	3.1	2.8	2.9
±SD	2.5	2.9	2.7	2.9	1.3	1.6	1.2	0.7

Abbreviations are as in table 2.

^AAngina pectoris.Significance vs resting values: ^Bp < .05; ^Cp < .005; ^Dp < .001.Significance vs exercise values: ^Ep < .05; ^Fp < .001.

wedge pressure.¹⁰ The authors concluded from their study that the handgrip test is associated with active vasoconstriction, probably due to reflex activation of the sympathetic nervous system, which could be suppressed by the use of coronary vasodilators such as nitroglycerin.

Matsuda et al.¹³ measured coronary stenosis and normal vessel diameters with monoplane angiograms during supine bicycle exercise in patients with exertional angina and either ST segment elevation or depression. All four patients with ST segment elevation had complete occlusion of an organic stenosis during exercise. Five of the seven patients with ST segment depression showed no substantial change in luminal diameter or in percent stenosis during exercise. The lack of exercise-induced vasoconstriction of stenosis in these five patients highlights the heterogeneity of the behavior of stenosis. Thirty percent of stenoses are concentric without a compliant normal vessel wall segment,^{8,9} and thus may not be capable of a dynamic response to exercise.

The purpose of our study was to evaluate the response of the epicardial coronary arteries to dynamic exercise and to examine the reaction of coronary artery stenosis to high-flow and high-demand situations in a preparation that is more physiologically accurate than Brown's handgrip stress test. In contrast to Matsuda's study,¹³ all of our patients had classic angina with no evidence of coronary artery spasm or ST segment elevation. Interestingly, we demonstrated narrowing of coronary artery stenosis in our first group of patients with coronary artery disease and exercise-induced angina pectoris. In contrast to what occurred during the handgrip test, normal coronary arteries dilated, probably due to vasoactive metabolic compounds and increased perfusion pressure during exercise.

Mechanism of narrowing of coronary artery stenosis. The mechanism of exercise-induced narrowing of a coronary stenosis remains unclear and represents a new and important observation in the pathophysiology of acute myocardial ischemia in patients with classic angina pectoris. Brown et al.¹ recently discussed the

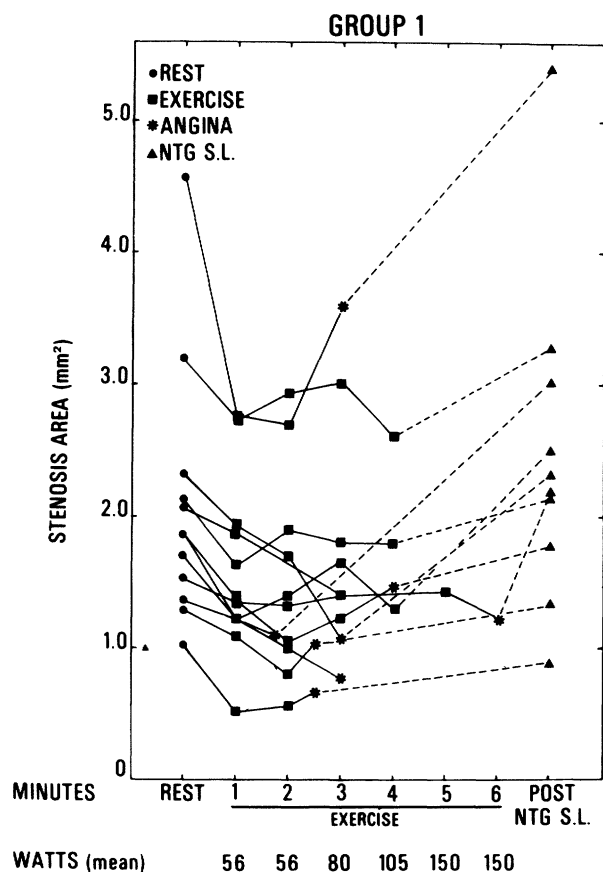


FIGURE 3. Cross-sectional area of stenosis (mm^2) at rest, at each minute during supine bicycle exercise, and after 1.6 mg sublingual nitroglycerin administered at the end of exercise in all 12 patients in group 1. During exercise, the stenoses became narrower in all patients, with dilation after sublingual nitroglycerin administered at the conclusion of the exercise test. Minutes = minutes of supine bicycle exercise; Watts = mean workload for patients at a given duration of exercise; NTG S.L. = sublingual nitroglycerin.

following possible mechanisms for narrowing of the coronary artery during exercise: (1) passive collapse of a stenotic vessel due to an exercise-induced increase in coronary blood flow (Venturi mechanism),^{12, 14, 15} and (2) active vasoconstriction arising from α -adrenergic stimulation by circulating catecholamines and activation of the sympathetic nervous system.^{16, 17}

Passive collapse. As blood flows through a coronary stenosis, its velocity increases while its pressure decreases to a minimum at the point of greatest narrowing.¹ Most of this pressure loss persists distal to the stenosis¹⁸ because of turbulence. Dynamic exercise increases coronary blood flow up to four times, which would increase the pressure gradient between the proximal coronary artery and the stenosis 16-fold,¹ thereby decreasing the distension pressure within the stenosis (Venturi mechanism).^{15, 19} Seventy percent of

significant coronary stenoses contain a normal wall segment within their circumference,^{8, 9} which has been shown to collapse in response to decreases in perfusion pressure.²⁰ According to this theory, the increased coronary blood flow during handgrip exercise may induce the Venturi mechanism, causing passive collapse of the stenosis. However, this appealing concept may be valid only in patients with severe coronary artery stenoses,¹² in whom flow velocity through the stenosis is already high in the resting state.

Active vasoconstriction. Isometric handgrip stress may precipitate active vasoconstriction through a reflex increase in systemic and local coronary adrenergic activity.¹⁰ Since circulating catecholamines^{21, 22} and sympathetic nervous system activity^{23, 24} increase dur-

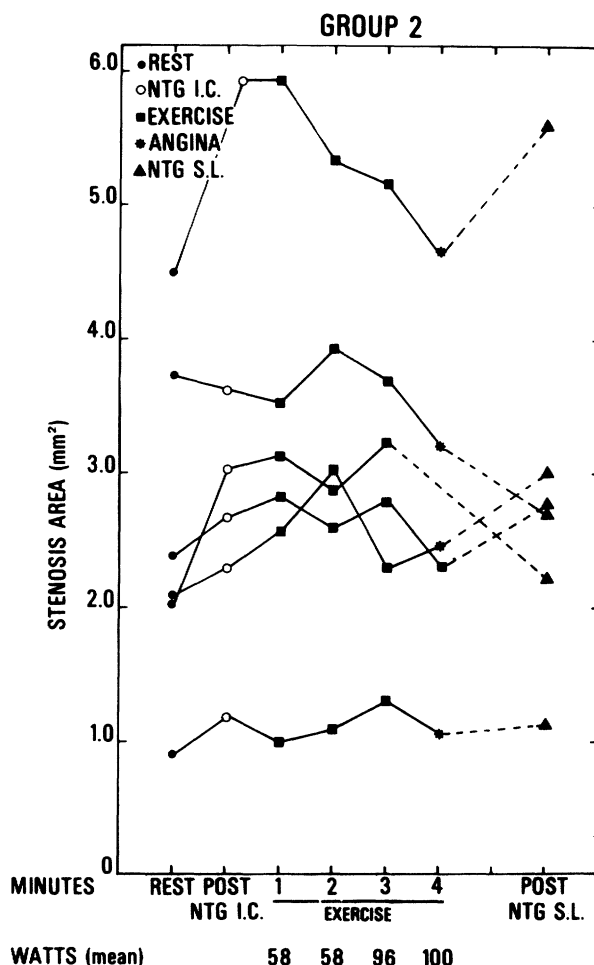


FIGURE 4. Cross-sectional area of stenosis (mm^2) at rest, after 0.1 mg intracoronary nitroglycerin, at each minute during subsequent supine bicycle exercise, and after 1.6 mg sublingual nitroglycerin administered at the end of exercise in all six patients in group 2. Intracoronary nitroglycerin dilated the stenoses, with little change during subsequent dynamic exercise. NTC I.C. = intracoronary nitroglycerin. Other notations are as in figure 3.

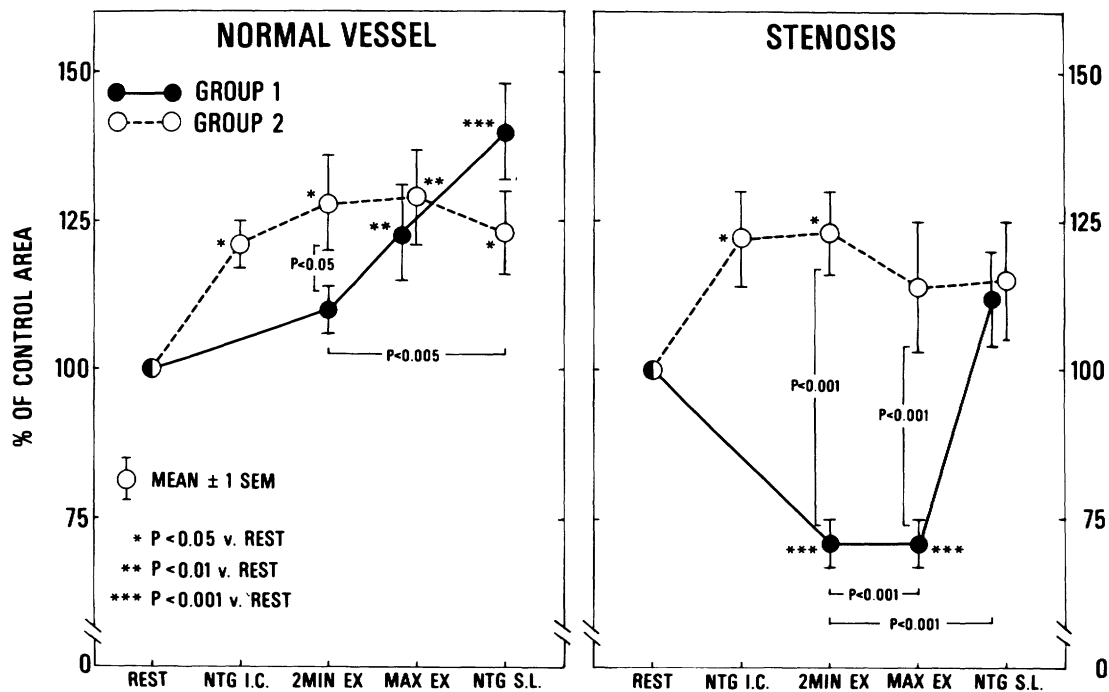


FIGURE 5. Responses of normal and stenotic coronary arteries to dynamic exercise in patients without (group 1) and with (group 2) pretreatment with intracoronary nitroglycerin, expressed as percent of resting luminal area. Normal vessels (*left*) dilated during exercise to 123% of control values, and were further dilated by sublingual nitroglycerin (140%). Intracoronary nitroglycerin induced dilation of normal vessels to 121% of resting values and dilation persisted at the same level during subsequent exercise (129%). In stenotic vessels (*right*), exercise induced a narrowing of stenoses to 71% of control, which dilated to 112% of resting values after sublingual nitroglycerin was given at the end of exercise. Intracoronary nitroglycerin administered to group 2 patients produced dilation of stenosis (122%) that persisted during exercise (114%), thereby preventing the exercise-induced narrowing of stenosis seen in group 1. 2MIN EX = 2 min of supine bicycle exercise; MAX EX = the end of symptom-limited exercise; other notations are as in figures 3 and 4.

ing dynamic exercise, it seems reasonable to expect active vasoconstriction in some patients with a history of vasospastic angina.¹³ However, the response to dynamic exercise of normal and stenotic coronary vessels in patients without vasospasm is less clear. During dynamic exercise, there is competition between α -receptor-mediated vasoconstriction produced by catecholamines^{24, 25} and by the sympathetic nervous system, and the vasodilative effect of increased perfusion pressure¹⁴ and metabolites such as adenosine.²⁶

Our data confirm that normal coronary arteries dilate during dynamic exercise (table 3 and figure 5), with an increase in coronary vessel area of 23%. In contrast, the stenotic vessel segments exhibited a decrease in area of about 30% during dynamic exercise. This behavior of the coronary stenoses was observed in every patient in our first study group. Since all patients in this study suffered from exercise-induced angina pectoris with no ST segment elevation and had no history of variant angina, the occurrence of active vasospasm causing total or subtotal coronary occlusion as in Prinzmetal's or vasospastic angina⁴ was highly unlikely.

To further elucidate the possible mechanism of narrowing of stenotic coronary arteries during dynamic exercise (passive collapse of the normal wall segment or active vasoconstriction), we administered intracoronary nitroglycerin to a second group of six patients to nullify the possible vasoconstricting effects of the subsequent exercise (table 3; figures 4 and 5). A dose of 0.1 mg nitroglycerin was given to cause changes in coronary artery caliber without systemic alterations in preload and afterload (table 2). After intracoronary nitroglycerin, an increase in luminal area was observed in the normal (+21%) as well as in the stenotic (+22%) arteries. However, during dynamic exercise no further dilation of the normal coronary arteries was observed, probably due to maximal vasodilation by nitroglycerin, and the stenotic coronary arteries were not observed to narrow during dynamic exercise as was observed in patients who did not receive intracoronary nitroglycerin (figures 1, 3, and 5). Apparently the vasodilating drug was able to eliminate the exercise-induced narrowing of the stenoses, suggesting that active vasoconstriction is responsible for this decrease in luminal area.

Recently, Holtz *et al.*²⁷ described, in the conscious dog, a flow-dependent, endothelium-mediated dilation of the epicardial coronary arteries that was also observed more than 50 years ago by Schretzenmayr,²⁸ who reported dilation of the canine femoral artery *in situ* in response to increments in flow through this artery. It is assumed that a endothelium-derived relaxing factor is responsible for dilation of the epicardial coronary arteries during increased flow states such as dynamic exercise. Since the stenotic segments showed no vasodilation but, in contrast, vasoconstriction during exercise, how can these observations be explained in the light of the above-mentioned mechanism of endothelium-mediated vasodilation? A hypothesis that could explain vasoconstriction at the site of the stenosis is that there is malfunctioning of the endothelium, resulting in a lack of the endothelium-derived relaxing factor. Thus, the direct constrictor action of circulating catecholamines on the stenotic section may predominate and cause an increased tendency to vasoconstriction.²⁹ Another possible explanation of vasoconstriction at the site of the coronary stenosis is that enhanced shear stress might induce thrombocyte aggregation with release of serotonin and thromboxane A₂, both of which induce vasoconstriction.^{30, 31}

A passive collapse of the free vessel wall seems to be unlikely in our group of patients because one would expect that an exercise-induced collapse would still occur after intracoronary nitroglycerin due to the passive nature of this mechanism. However, passive collapse is most likely to occur in patients with severely stenosed coronary arteries (arteries with a minimum area of less than 1 mm²).¹ Thus, our data might not provide an adequate answer to this question. Since a narrower stenosis has a greater potential for inducing passive collapse, we compared exercise-induced changes in stenotic area in patients with similar luminal areas (range 2.1 to 3.2 mm²) when measured just before exercise — at rest in group 1 (patients 1, 8, 11, and 12) and after intracoronary nitroglycerin in group 2 (patients 14, 15, and 17) (table 3). When these patients with similar luminal areas of stenosis were compared there was still no narrowing of the stenotic vessel during exercise after intracoronary nitroglycerin. Because the increase in mean aortic pressure during exercise was significantly greater in group 1, these stenoses may have been more liable to sustain passive collapse than those of group 2 patients. However, in patients in each group with the same amount of exercise-induced increase in aortic diastolic pressure (5 to 17 mm Hg) the results were the same as for each group taken as a whole (figure 6).

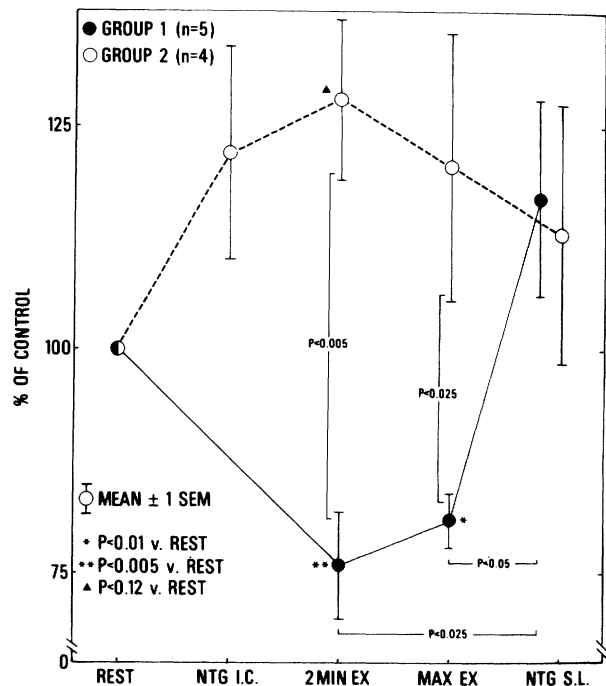


FIGURE 6. Responses of coronary artery stenosis to exercise and nitroglycerin in selected patients from groups 1 and 2 with a similar increase (5 to 17 mm Hg) in aortic diastolic pressure during exercise. The results are presented as in figure 5, as percent of luminal area of stenosis at control. Comparison of these subgroups was made to control for the higher exercise-induced increase in mean aortic pressure in group 1 than in group 2. Because a greater increase in perfusion pressure at the coronary stenosis has a greater potential to cause passive collapse of the stenotic vessel (Venturi mechanism), it is interesting that in these patients with similar increases in aortic diastolic pressure during exercise the results are similar to those in each group as a whole (figure 5). Notations are as in figure 5.

The basic hemodynamic changes were also comparable in the two groups of patients: the rate-pressure product and the occurrence of myocardial ischemia (as indicated by a significant increase in mean pulmonary arterial pressure) observed with angina pectoris were similar in two-thirds of the patients in both groups. The rate-pressure product was, however, significantly lower in both groups during the intracatheterization exercise test mainly due to the following two mechanisms:

(1) It is well known³² that during supine bicycle exercise development of angina occurs earlier than during upright position because venous return, and therefore filling pressure, is higher in individuals in the supine position. This results in increased wall stress and oxygen consumption by the left ventricle. Therefore, a reduction of 30% of the predicted work capacity in patients in the supine position is reasonable.

(2) Intracatheterization rate-pressure product is calculated from systolic aortic pressure measured directly with the Judkins coronary catheter, whereas the rate-pressure product during upright exercise is calculated

from cuff-measured systolic blood pressure, which generally tends to overestimate central systolic aortic blood pressure.

The increase in mean pulmonary arterial pressure was significantly less during exercise in group 2 than in group 1 (table 2) due to the intracoronary administration of nitroglycerin. Another apparent beneficial effect of preexercise intracoronary nitroglycerin was that these patients were able to perform at the same percentage of their predicted work capacity during the catheterization supine bicycle test as during baseline upright bicycle exercise (table 1). Those patients not pretreated with nitroglycerin achieved a significantly lower percentage of their predicted work capacity than had been attained previously. This difference might be due to patient selection, but is probably due to the anti-ischemic action of intracoronary nitroglycerin.

Limitations of the study. The computer-assisted quantitation of biplane coronary angiograms is probably the best available technique for measuring coronary artery stenoses in man. This technique has been shown by others by measurements of known dimensions to be accurate to within 0.08 mm.³³ The changes observed in our study, such as the 0.6 mm² decrease in area of stenosis during exercise, are clearly larger than the resolution of the technique. Furthermore, interobserver variability has been shown to be small, ranging from the 3% variability reported by Gensini et al.³⁴ to the 0.12 mm² or 17% of the minimal area of very severe stenoses reported by Brown et al.³³ Interobserver variability in the measurements of the luminal areas of a broad range of stenoses and normal vessels in our study was 9.3% for monoplane and 7.9% for biplane determinations and 12.4% for monoplane vs biplane measurements. Although the observed changes in areas of coronary vessels during exercise were small, the technique seems to be adequate for reliable quantitation of coronary artery stenoses.

Clinical implications. We observed narrowing of coronary stenosis during dynamic exercise. Thus, myocardial ischemia is induced not only by the imbalance of oxygen supply and demand caused by a fixed coronary stenosis, but is aggravated by vasoconstriction. Consequently, the treatment of coronary artery disease manifested as classic angina should not be limited to attempts at the reduction of myocardial oxygen demand by changing preload, afterload, and contractility. The therapeutic benefit must be extended to include vasodilation of coronary stenosis so that dynamic reductions in blood flow and oxygen supply can be inhibited. This concept is not only valid for the treatment of patients with vasospastic angina, but is

equally useful in the treatment of those with classic exercise-induced angina pectoris. In these latter patients, nitroglycerin¹⁰ and calcium blockers³⁵⁻³⁷ can prevent exercise-induced vasoconstriction of stenosis, thereby improving exercise capacity and reducing myocardial ischemia.

In summary, in patients with classic angina pectoris, dynamic exercise caused a reduction in cross-sectional area of stenosis, while luminal area of normal vessels increased. Preexercise intracoronary nitroglycerin dilated both stenotic and normal vessels, and there was no narrowing of stenosis during dynamic exercise. This suggests that exercise-induced narrowing of stenosis is the result of active vasoconstriction that probably occurs in the normal vessel wall segment contained within the circumference of most stenoses. The lack of exercise-induced constriction of stenosis was associated with lessened left ventricular ischemia and preservation of work capacity. Thus, active vasoconstriction of a coronary artery stenosis can be an important mechanism in producing myocardial ischemia during dynamic exercise.

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