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Research Article

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Persistence of Regional Left Ventricular Dysfunction after Exercise-induced Myocardial Ischemia

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Abstract

To determine whether regional myocardial dysfunction occurring after exercise-induced ischemia might be caused by continued abnormalities of myocardial blood flow in the post-exercise period, nine dogs were instrumented with ultrasonic microcrystals for determination of circumferential segment shortening, circumflex artery electromagnetic flow probes, and hydraulic coronary artery occluders. Dogs performed treadmill exercise during partial inflation of the coronary artery occluder. When the stenosis was maintained after exercise (persistent stenosis), subendocardial hypoperfusion was noted 1 min after exercise (subendocardial flow = 0.79±0.42 ml/min per g vs. 1.39±0.43 ml/min per g control), and this was associated with continued dysfunction in the ischemic zone (segment shortening 45.4±36.9% of resting control). When the stenosis was released immediately after exercise (temporary stenosis), however, flow was markedly increased 1 min post-exercise (mean transmural flow 4.24±1.22 ml/min per g; subendocardial flow 4.18±1.52 ml/min per g), and this was associated with a transient increase in segment shortening to 104.5±9.3% of resting control. 5 min after exercise, however, moderate reductions in ischemic segment shortening were noted after both temporary stenosis and persistent stenosis runs, and these persisted for 30 min post-exercise. It is concluded that regional left ventricular dysfunction may persist for a significant period of time after exercise-induced ischemia. Furthermore, early after exercise, dysfunction is related to persistent abnormalities of myocardial blood flow, whereas late after exercise it is independent of primary reductions in myocardial blood flow.

Introduction

Regional myocardial dysfunction may persist after release of transient coronary artery occlusions insufficient in duration to cause myocardial necrosis (1–4). Although this phenomenon has been well characterized using brief coronary artery occlusions as the ischemic stimulus, ischemia more often occurs clinically when a coronary artery stenosis prevents appropriate increases in blood flow during exercise or other stress. Although it has been previously shown that regional dysfunction may occur after exercise in the presence of coronary artery stenosis (5), the mechanisms underlying post-exercise dysfunction have received little attention. In the presence of a flow-limiting coronary artery stenosis, exercise results in an alteration of the transmural distribution of myocardial perfusion such that flow is distributed preferentially to the subepicardium, while the subendocardium is most severely hypoperfused (6). Since distal coronary vasodilation and tachycardia may persist for some time after the cessation of exercise, it is possible that persistent subendocardial hypoperfusion would continue during the early post-exercise period. Thus, regional dysfunction after exercise might be due either to persistent subendocardial ischemia or to the residual effects of prior ischemia on post-ischemic myocardium. To determine whether perfusion abnormalities persisting after exercise contribute to post-exercise dysfunction, a chronically instrumented canine preparation was used to study regional function after exercise-induced ischemia in the presence and absence of coronary artery stenosis in the post-exercise period.

Methods

Studies were performed on nine adult mongrel dogs previously trained to run on a motor-driven treadmill. The animals were anesthetized with pentobarbital sodium (25–30 mg/kg i.v.) and ventilated with a Harvard respirator. A left thoracotomy was performed in the fourth intercostal space. A polyvinyl chloride catheter (3.0 mm o.d.) filled with heparin saline solution (200 U/ml) was inserted into the root of the aorta via the internal thoracic artery for pressure monitoring and blood withdrawal. The pericardium was then incised and the heart supported in a pericardial sling. The proximal 1.5 cm of the circumflex artery was dissected free and an electromagnetic flow probe and hydraulic occluder were fitted around it. A chronically implantable micromanometer (Konigsberg P-5, Konigsberg Instruments, Inc., Pasadena, CA) and a fluid-filled polyvinyl catheter were then inserted into the left ventricle through the apical dimple. Two pairs of ultrasonic microcrystals were inserted for measurement of circumferential segment shortening. The crystals of each pair were placed 1.0–2.0 cm apart in the inner one third of the left ventricular wall, and oriented circumferentially. One crystal pair was placed in the vascular distribution of the circumflex coronary artery, and the other in the distribution of the left anterior descending coronary artery. A fluid-filled polyvinyl chloride catheter was inserted into the left atrial cavity via the left atrial appendage and secured with a purse string suture. The pericardium was loosely closed, and all catheters and electronic cables were tunneled dorsally to the base of the neck, where they were exteriorized. The thoracotomy was then repaired and the animals allowed to recover from surgery.

All experiments were performed 7–10 d postoperatively when the animals were in good physical condition. Catheters were protected with a nylon vest that the dogs had been trained to wear (Alice King Chatham, Los Angeles, CA). Measurements of aortic and left ventricular pressures were obtained using fluid-filled catheters connected to Statham P-23Db pressure transducers fastened to the nylon vest at the midchest level. Left ventricular pressure and dP/dt were determined from the implanted micromanometer which was calibrated to the fluid-filled left ventricular pressure catheter. Circumflex coronary artery blood flow was measured with a Statham SP2202 electromagnetic flowmeter. Ultrasonic microcrystal measurements of circumferential segment length were obtained by activating the implanted piezoelectric crystals with a Schuessler and Assoc. (Cardiff by the Sea, CA) ultrasonic dimension system (model 401, modified so as not to interfere with electromagnetic flowmeter function). All data were recorded on an eight-channel direct writing oscillograph (model 8800; Hewlett-Packard Co., Palo Alto, CA).

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Myocardial blood flow was measured with serial injections of microspheres, 15 μm in diameter, labeled with gamma-emitting nuclides (^{125}I, ^{141}Ce, ^{51}Cr, ^{85}Sr, ^{95}Nb, ^{113}Sn, and ^{46}Sc). Before injection, the microspheres were agitated for at least 15 min in an ultrasonic bath. During each intervention, 3×10^6 microspheres were injected into the left atrial catheter over a 15-s interval, and the atrial catheter was flushed with 10 ml of isotonic saline. Beginning 5 s before each microsphere injection and continuing for 90 s, a reference sample of blood was withdrawn from the aortic catheter at a constant flow rate of 15.0 ml/min.

Before each study, the dogs underwent a warm-up exercise period ~5 min in duration, during which time the exercise level required to achieve heart rates of 200–240 beats/min was determined. After warm-up exercise, 30 min was allowed for the dog to return to preexercise control levels of heart rate, arterial pressure, and left ventricular dP/dt. Hemodynamic and ultrasonic dimension data were then recorded and microspheres were injected into the left atrium for determination of resting regional myocardial blood flow. Normal saline was then instilled into the hydraulic occluder using a mechanical balloon inflation device (7) that permitted controlled inflation of the occluder. A level of stenosis was achieved that reduced resting myocardial blood flow <20%, but did not result in hemodynamic alterations or a reduction in ischemic segment shortening. This level of circumflex coronary artery stenosis was then used for all exercise interventions. Repeat resting hemodynamic and ultrasonic dimension data were then recorded in the presence of the circumflex stenosis, and a second microsphere injection was performed during resting conditions with the stenosis applied. One of two exercise protocols was then performed. Each dog underwent both exercise protocols on successive days and the order of the protocols was randomized for each dog. In protocol 1 (persistent stenosis) the dog was exercised at the previously determined treadmill speed and grade, sufficient to raise the heart rate to 200–240 beats/min. The dog maintained exercise at this stable level for 10 min. 5 min into the exercise period, an additional injection of radioactive microspheres was made into the left atrium for determination of myocardial blood flow during exercise in the presence of a stenosis. The dog continued exercising at the same level of exercise for an additional 5 min. The treadmill was then stopped, and an additional set of radioactive microspheres injected 1 min after cessation of exercise. Hemodynamic and ultrasonic dimension data were recorded continuously throughout exercise and for 0.5 h after exercise (Figs. 1 and 2). At 20 min after exercise, the circumflex coronary artery stenosis was released. This resulted in a brief reactive hyperemia of very little magnitude. The dogs were then removed from the treadmill, placed in a sling to maintain upright posture, and allowed to rest quietly in a darkened laboratory. Hemodynamic and ultrasonic microcrystal data were then recorded at 15-min intervals thereafter for 2 h post-exercise.

On the alternate day, exercise protocol 2 (temporary stenosis) was performed. A period of warm-up exercise, 30-min rest period, and 10-min exercise period were identical to protocol 1. Immediately after exercise, however, the stenosis was released, permitting unimpeded circumflex artery flow throughout the post-exercise period. Again, radioactive microspheres were injected 1 min after cessation of exercise for measurement of regional myocardial blood flow. Hemodynamic and ultrasonic dimension data were recorded for 2 h after completion of exercise, as previously described. During the warm-up run on the second day, radioactive microspheres were also injected into the left atrium for measurement of regional myocardial blood flow during exercise in the absence of a critical coronary artery stenosis.

After the study had been completed, the dogs were killed with a lethal dose of pentobarbital sodium. A left thoracotomy was then performed and the heart and both kidneys excised. The circumflex coronary artery was cannulated at the site of the hydraulic occluder and 10 ml of Evans blue dye injected to identify the area of the left ventricle supplied by the circumflex coronary artery distal to the site of stenosis. The heart was then weighed and fixed in 10% buffered formalin. After fixation, the atria, right ventricle, and aorta were removed and the left ventricle weighed. The pairs of ultrasonic microcrystals were then inspected to ensure that all pairs of ischemic crystals were located at least 1 cm within the perfusion boundary of the circumflex coronary artery, identified by blue stained myocardium, and that all nonischemic pairs were at least 1 cm outside the perfusion boundary of the circumflex coronary artery. Pairs of ultrasonic microcrystals with the interposed myocardium were then excised, and the myocardium divided into four layers from epicardium to endocardium. Myocardial samples were then weighed on an analytical balance and placed in vials for determination of radioactivity. Myocardial and blood reference specimens were counted in a gamma counting system (model 5912; Hewlett-Packard Co.) with a multichannel analyzer at window settings corresponding to peak energies of each radionuclide. The activity recorded at each energy window was corrected for background and for overlapping counts contributed by accompanying isotopes according to the method of Domenech et al. (8).

Blood flow to each myocardial specimen was computed as $Q_m = Q_r \cdot C_m/C_r$, where Q_m is the myocardial blood flow (milliliters per

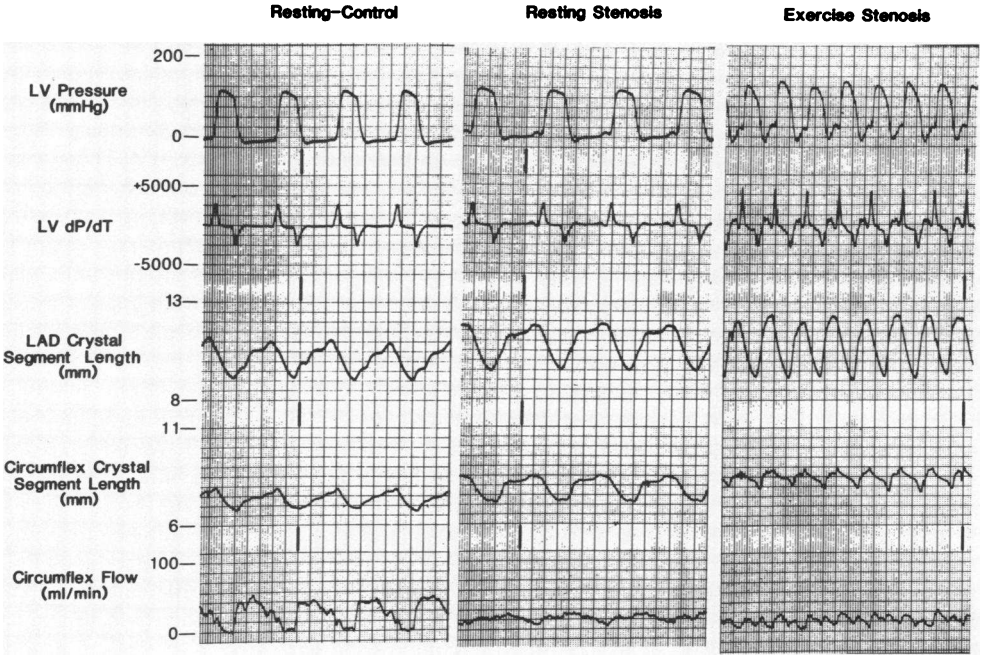

Figure 1. Recordings obtained during control resting conditions, with circumflex coronary stenosis under resting conditions, and during exercise with circumflex stenosis. LVSP, left ventricular pressure (mmHg); LV dP/dt, left ventricular dP/dt (mmHg/s). Circumflex and left anterior descending segment length in millimeters, circumflex artery flow in milliliters per minute. After coronary stenosis at rest there is slight decrease in circumflex flow but no decrease (in this instance, a small increase) in circumflex segment shortening. During exercise in the presence of the same stenosis, however, there is a marked decrease in circumflex segment shortening; LAD segment shortening has increased.

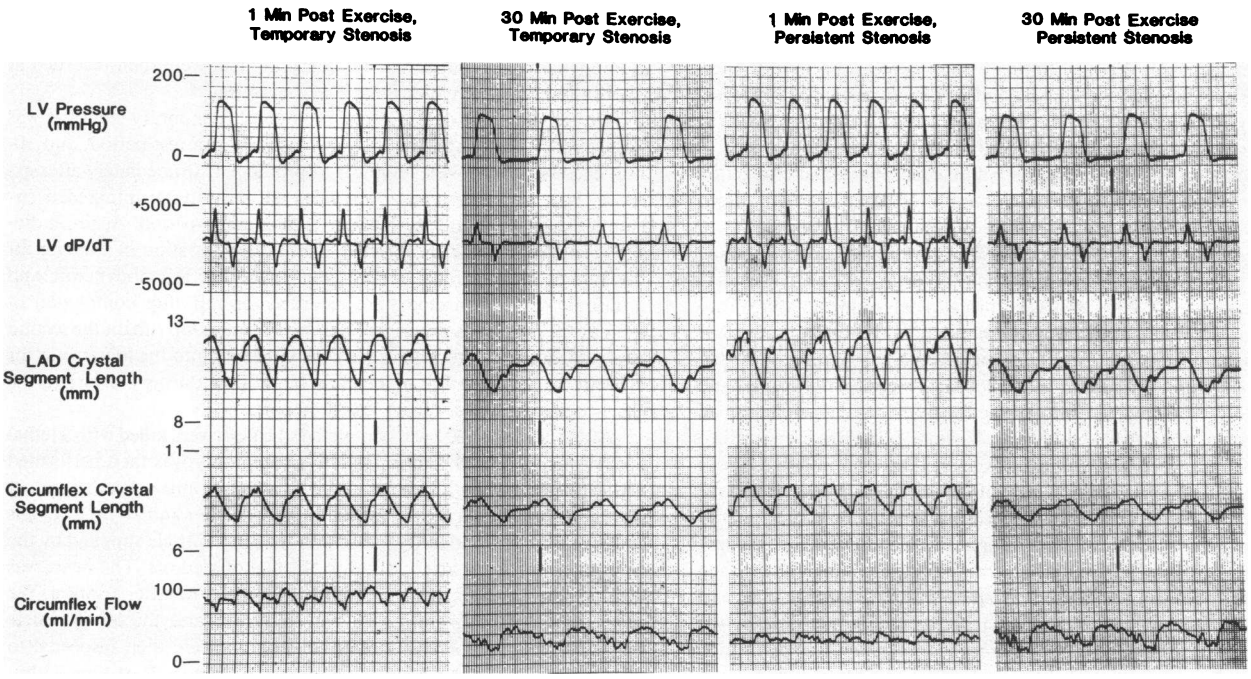

Figure 2. Recordings obtained 1 and 30 min after exercise with transient and persistent stenosis. Abbreviations as in Fig. 1. At 1 min after exercise with stenosis released, segment shortening is above control levels, and >1 min after exercise with persistent stenosis. By 30 min after exercise, circumflex segment shortening is comparable between the two runs.

minute), Q_r is the reference blood flow rate (milliliters per minute), C_m is the counts per minute of the myocardial specimen, and C_r is the counts per minute of the reference blood specimen. Blood flow was divided by the sample weight and expressed as milliliters per minute per gram of myocardium. The ratio of subendocardial flow to subepicardial flow was obtained by dividing flow to the innermost layer by the corresponding flow to the epicardial layer.

For ultrasonic microcrystal determination of circumferential segment length, the end-diastolic segment length was measured at the initiation of the upstroke of the left ventricular pressure tracing recorded by the Konigsberg micromanometer (Konigsberg Instruments, Inc.), and the end systolic segment length was measured 20 ms before peak negative dP/dt on the differentiated left ventricular pressure tracing (9). The values for 10 successive beats were averaged. Percent segment shortening was defined as end-diastolic length minus end-systolic length divided by end-diastolic length. Circumflex flow measurements were obtained using a Gould Statham SP2202 electromagnetic flow meter. The volume of antegrade circumflex coronary artery flow was determined by electrical integration of the electromagnetic flowmeter tracing.

Hemodynamic, myocardial blood flow, and ultrasonic dimension data were compared using multivariate analysis of variance. When an overall difference was found, individual comparisons were made using the paired t test with the Bonferroni correction for multiple simultaneous comparisons. By 2 h postexercise, most dogs were sleeping. This was associated with a slight decrease in regional function, even in nonischemic segments. In order to estimate recovery time to "control" function, therefore, function in ischemic and nonischemic segments was compared at each time period. When function in ischemic and nonischemic segments no longer differed, function was assumed to be back to control. Unless otherwise specified, values are reported as mean±SD.

Results

In one dog, ultrasonic microcrystal signals were inadequate; thus, complete hemodynamic, myocardial blood flow and regional function data were obtained in eight animals. In no animal was there evidence of myocardial necrosis by gross pathological examination.

Hemodynamics. Hemodynamic data are summarized in Table I. The resting heart rate averaged 134±20 beats/min, and did not change after the application of the coronary artery stenosis at rest. During exercise in the absence of coronary artery stenosis, heart rate increased to 237±16 beats/min. In the presence of coronary artery stenosis, similar heart rates were achieved at the same work load (236±20 beats/min). There was a tendency for lower systolic aortic pressure to occur during exercise in the presence of coronary artery stenosis compared with exercise in the absence of stenosis, although this was not statistically significant. The left ventricular end-diastolic pressure was significantly higher during exercise in the presence of coronary artery stenosis compared with exercise in the absence of coronary artery stenosis or during resting conditions ($P < 0.005$). There were no differences in the heart rate, aortic pressure, left ventricular end-diastolic pressure, or left ventricular dP/dt during or after exercise runs with persistent stenosis vs. temporary stenosis. Following cessation of exercise, there was a prompt initial decrease in heart rate that was not different from control by 30 min post-exercise. Aortic pressure, left ventricular end-diastolic pressure, and left ventricular dP/dt all returned to control values by 15 min after exercise.

Regional myocardial blood flow. Mean transmural flow and blood flow to each myocardial layer are depicted in Figs. 3 and 4. Mean transmural blood flow at rest was similar in the left anterior descending and circumflex regions (1.21±0.28 vs. 1.21±0.24 ml/min per g). During resting conditions, the transmural distribution of perfusion significantly favored blood flow to the subendocardium (see Table II). During exercise in the absence of coronary artery stenosis, flow increased to similar levels in both circumflex and left anterior descending regions

Table I. Hemodynamic Data at Rest, during, and after Exercise

	Resting control	Resting + stenosis	Control exercise	Exercise + stenosis		1 min postexercise		15 min postexercise		60 min postexercise	
				TS	PS	TS	PS	TS	PS	TS	PS
HR	134	137	237	236	237	179	183	159	158	149	136
(*beats/min*)	±20	±15	±16	±20	±20	±23	±17	±33	±21	±31	±16
LVSP	124	127	167	155	156	136	134	120	115	118	118
(*mmHg*)	±11	±20	±24	±19	±14	±14	±20	±18	±9	±18	±21
LVEDP	4.2	5.6	8.3	23	19	10	13	6.9	8.9	5.6	3.9
(*mmHg*)	±3.3	±3.8	±7.8	±8.2	±4.1	±6.6	±3.5	±6.4	±3.6	±5.7	±3.8
LV d*P*/d*t*	2,400	2,320	4,310	4,090	3,700	3,120	2,540	2,230	2,350	2,200	2,100
(*mmHg/s*)	±440	±580	±1,070	±420	±830	±1,110	±370	±700	±420	±650	±320
AODP	78	80	94	77	66			79	77	69	79
(*mmHg*)	±18	±19	±23	±12	±28	—	—	±17	±8	±11	±13

HR, heart rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; AODP, aortic diastolic pressure; TS, temporary stenosis; PS, persistent stenosis. Values are expressed as mean±SD. There were no significant differences between TS and PS for any hemodynamic variable.

(2.60±0.71 vs. 2.83±0.7 ml/min per g). Again, flow favored subendocardial regions. During circumflex artery stenosis at rest, mean transmural flow to circumflex regions was unchanged (1.21±0.28 vs. 1.03±0.29 ml/min per g). Although flow to the subendocardium appeared somewhat lower, neither subendocardial flow nor the ratio of subendocardial to subepicardial flow differed between control and stenosis at rest.

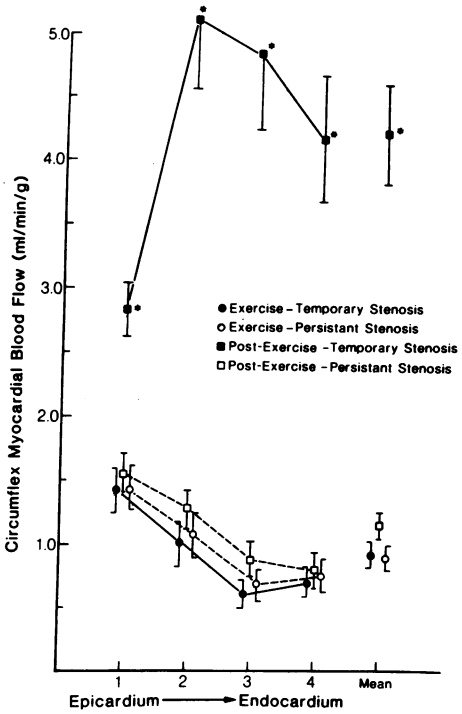

Figure 3. Myocardial blood flow±SE to four transmural layers of circumflex myocardium is shown during and 1 min after exercise for both persistent stenosis and temporary stenosis runs. * denotes significant differences between temporary stenosis and persistent stenosis ($P < 0.01$).

During exercise in the presence of coronary artery stenosis, a significant maldistribution of myocardial blood flow occurred in circumflex regions; flow to subepicardial layers increased slightly above resting control values, whereas flow to subendocardial layers decreased from base line (see Fig. 3). Thus, the transmural distribution of myocardial blood flow now favored the subepicardium (Table II). Flow during exercise with temporary stenosis and exercise with persistent stenosis was similar. 1 min after exercise there was a marked difference between the temporary stenosis and persistent stenosis runs, however. When coronary artery stenosis was released immediately after exercise, flow to the circumflex regions increased dramatically; although flow was highest in the midwall, it increased significantly in all four layers and subendocardial flow again exceeded subepicardial flow (Table II). In the presence of continued stenosis 1 min after exercise, however, the mean transmural flow remained at control levels with persistence of subendocardial hypoperfusion.

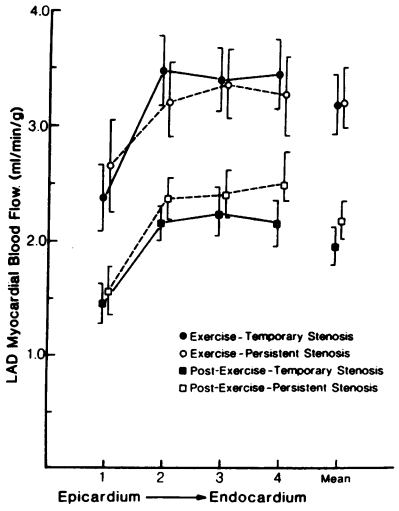

Figure 4. Myocardial blood flow±SE to the four transmural layers of LAD distribution myocardium is shown during and 1 min after exercise for both persistent stenosis and temporary stenosis runs.

Table II. Ratio of Subendocardial to Subepicardial Blood Flow

	Control	Control + stenosis	Exercise (no stenosis)	Exercise with stenosis		1 min postexercise	
				TS	PS	TS	PS
Circumflex	1.41±0.19	1.19±0.40	1.62±0.32	0.51±0.24	0.48±0.29	1.58±0.88	0.63±0.44*
LAD	1.56±0.37	1.59±0.25	1.57±0.40	1.37±0.42	1.68±0.45	1.50±0.36	1.64±0.42

Values are mean±SD. TS, temporary stenosis runs; PS, permanent stenosis runs. * TS significantly different from PS; $P < 0.01$.

Fig. 5 summarizes circumflex coronary artery flow, as determined by electromagnetic flowmeter, at rest, during exercise, and after exercise. Circumflex flow was reduced slightly, but not significantly, during exercise in the presence of stenosis. 1 min after exercise with temporary stenosis, a marked increase in circumflex flow was observed. Although still substantially elevated 5 min after exercise, this was no longer statistically different from control. Following release of stenosis at 20 min after exercise with persistent stenosis, flow increased slightly, but again not significantly.

Regional myocardial function. Segment shortening data at rest and during exercise are presented in Table III. Resting percent segment shortening averaged 15.5±2.8 for circumflex segments, and 16.1±4.2 for left anterior descending (LAD)[1] crystal pairs. During exercise in the absence of coronary stenosis, percent segment shortening increased similarly in both anterior descending (19.4±2.7%) and circumflex crystal pairs (19.7±5.5%). The application of circumflex coronary artery stenosis under resting conditions did not significantly alter resting percent segment shortening in either the anterior descending (16.3±3.0%) or circumflex crystal pairs (14.9±3.5%). When the circumflex stenosis was maintained during exercise, however, percent segment shortening was significantly decreased in the circumflex crystal pairs to ~40% of the resting value. Segment shortening was depressed to a similar extent during temporary stenosis and persistent stenosis runs. During exercise in the presence of circumflex stenosis, percent segment shortening of anterior descending crystal pairs increased to values above those observed during exercise in the absence of coronary artery stenosis, although this was not statistically significant. Circumflex percent segment shortening remained below resting control for 30 min following exercise after both temporary and persistent stenosis runs. 1 min after temporary stenosis runs, however, segment shortening had rebounded to slightly above control values (14.9±3.5 vs. 14.0±2.8%), whereas 1 min after persistent stenosis runs percent segment shortening remained well below control (7.5±5.8 vs. 15.0±3.8%).

Data summarizing normalized regional mechanical performance during recovery from exercise are depicted in Figs. 6 and 7. Percent segment shortening at each time period is normalized to a resting control value of 100. With exercise, circumflex segment shortening during temporary stenosis and persistent stenosis runs was depressed to a similar degree. 1 min after exercise, with temporary stenosis, an initial prompt return to base-line function was noted, such that segment shortening at 1 min after exercise was 104.5±9.3% of base line (not significantly different from control). Subsequently, however, there was deterioration in percent segment shortening, so that 5 min after exercise, segment shortening had fallen to 73.3±10% of base line. Thereafter, segment shortening gradually recovered so that by 30 min after cessation of exercise, segment shortening in anterior descending and circumflex regions were similar. As shown in Fig. 6, a strikingly different pattern occurred when coronary artery stenosis was maintained following cessation of exercise. 1 min after exercise with persistent stenosis, regional segment shortening remained markedly depressed at 45.4±36.9% of control value. By 5 min after cessation of exercise, however, there was no difference between segment shortening in those runs with persistent coronary artery stenosis compared with those runs where coronary artery stenosis had been released immediately after exercise. In both temporary stenosis and persistent stenosis runs, there was a persistent moderate reduction in regional function. Function gradually returned to normal by 30 min after exercise.

Nonischemic shortening during and early following temporary stenosis and persistent stenosis runs was similar. Segment shortening 15 min after persistent stenosis runs was reduced compared with temporary stenosis runs (see Fig. 7), but not compared with preexercise control (Table III). There were no hemodynamic differences between these two runs at this time period, and as previously noted, there was no difference in regional myocardial function in the ischemic zone at this time period.

Discussion

The purpose of this study was to characterize the relationship between myocardial blood flow and regional mechanical function following exercise-induced ischemia. It was found that regional dysfunction persisted for 15–30 min after exercise, pursuing a different time course of normalization than most hemodynamic

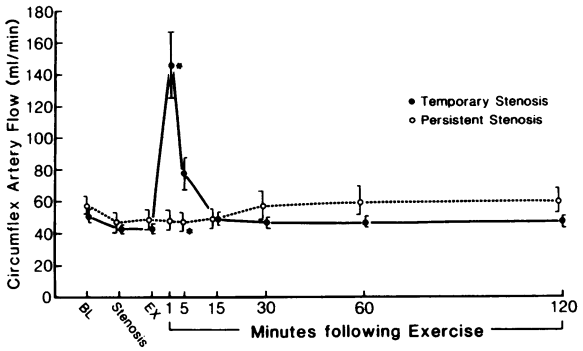

Figure 5. Circumflex coronary artery flow is shown at rest, at rest with stenosis, during exercise in the presence of stenosis, and for 120 min after stenosis. At 1 min after exercise, circumflex flow was significantly greater than control for temporary stenoses runs. * denotes significant difference ($P < 0.05$) from base line. BL, baseline.

1. *Abbreviation used in this paper:* LAD, left anterior descending.

Table III. Percent Segment Shortening during and After Exercise-induced Ischemia

			Minutes after exercise					
	BL	EX	1	5	15	30	60	120
Ischemic segment								
PS	15.0±3.8	5.9±3.1*	7.5±5.8*	10.2±5.3	10.5±3.5*	10.7±4.3*	12.3±3.3	13.2±4.0
TS	14.0±2.8	5.7±4.2*	14.9±3.5	10.2±1.9*	8.6±1.8*	9.7±2.0*	9.8±2.3	11.0±3.7
Nonischemic segment								
PS	15.5±3.7	21.8±5.5*	20.1±4.7*	14.3±4.9	14.6±4.4	14.6±4.4	14.5±3.8	14.6±3.6
TS	15.0±3.3	22.2±5.4*	19.7±6.4	18.2±5.0	16.8±4.6	16.5±3.1	16.9±5.5	14.8±4.3

* $P < 0.05$ compared with base line. PS, persistent stenosis. TS, temporary stenosis. BL, base-line resting without stenosis. EX, exercise with stenosis.

variables. Secondly, it was observed that in the presence of a coronary artery stenosis, persistence of regional dysfunction early after exercise was attributable to continued abnormalities of regional myocardial blood flow, whereas dysfunction late after exercise was independent of primary reductions in coronary artery flow.

In this study, exercise in the presence of limited coronary arterial inflow resulted in an abnormal transmural distribution of regional myocardial blood flow; subepicardial flow rose slightly above resting control values, while flow to deeper myocardial layers was decreased. This is consistent with previous observations using hydraulic occluders to create coronary artery stenoses (6, 10) or ameroid constrictors to create coronary occlusions (11–15). The mechanisms by which flow decreases to subendocardial layers include an increase in the fraction of total flow which occurs during systole (16), intense vasodilation of coronary resistance vessels, and reductions in distal coronary artery perfusion pressure (17). These alterations in the transmural distribution of myocardial blood flow have been associated with reduced mechanical performance of affected myocardium during exercise in this and previous studies (10, 13–15).

The relationship between abnormalities of myocardial blood flow and regional function during the post-exercise period has not previously been examined. That component of the maldistribution of transmural myocardial blood flow that is dependent on the relative amount of total flow occurring during systole would be expected to be related to heart rate. Although heart rates fell rapidly after exercise, heart rate remained somewhat elevated at 15 min following exercise compared with control. The time course of vasodilation of coronary resistance vessels and reduction in distal coronary artery pressure is unknown, but could contribute to persistent abnormalities of myocardial blood flow distribution in the post-exercise period.

The predominant experimental model of coronary artery disease used to study myocardial blood flow and regional function during exercise has been the ameroid occluder. Variable durations of dysfunction (1–30 min) have been noted after exercise in studies using this model (14, 15, 18, 19) and may reflect differences in exercise intensity and duration, and extent of collateral flow during and after exercise. Regional myocardial blood

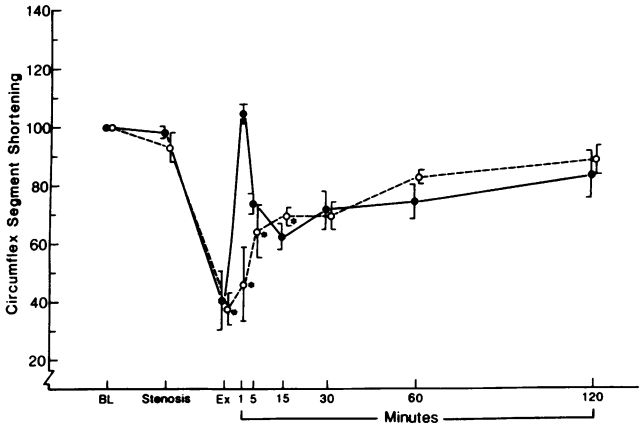

Figure 6. Circumferential segment shortening (normalized to base-line values of 100)±SE for circumflex crystal pairs with stenosis at rest, during, and after exercise. At 1 min after exercise, temporary and persistent stenosis runs differed significantly ($P < 0.01$). * denotes significant difference between ischemic and nonischemic segments ($P < 0.05$). Circumflex and LAD circumferential segment shortening were no longer different by 30 min after exercise. ●, Temporary stenosis; ○, persistent stenosis.

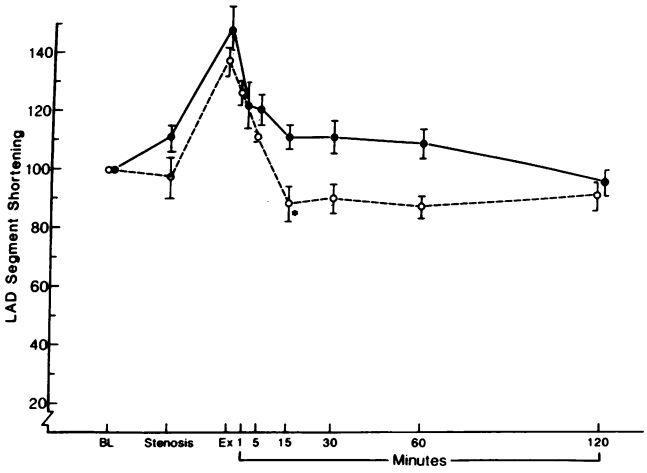

Figure 7. Circumferential segment shortening (normalized to baseline value of 100)±SE for LAD crystal pairs, with stenosis at rest, during, and after exercise. * Denotes significant difference between temporary stenosis and persistent stenosis runs ($P < 0.05$). ●, Temporary stenosis; ○, persistent stenosis.

flow post-exercise was not measured in these studies, however, and therefore the functional abnormalities observed in the post-exercise period might have reflected continued hypoperfusion of deeper myocardial layers and not persistent functional abnormalities resulting from previous exercise-induced ischemia.

The current study employed a hydraulic occluder to create a critical coronary artery stenosis. Thus, flow to ischemic myocardium during exercise came both from collateral channels and through the stenosed circumflex coronary artery. Thus, this experimental model simulates exercise in the presence of coronary artery stenosis, and also permits modulation of myocardial blood flow in the post-exercise period. Tomoike et al. (5) used a similar model to assess regional mechanical performance during brief, extremely intense exercise. A coronary stenosis more severe than that employed in this study was used, which lowered coronary flow ~50% but did not cause significant resting dysfunction. This remained in place for 10 min after exercise; at that time, function had recovered to 81% of the control value. Function was not further monitored, and regional myocardial blood flow was not measured in that study. In the current study, a coronary artery stenosis that did not significantly decrease mean resting blood flow was employed. Mean transmural flow did not appreciably increase during exercise, indicating that the contribution of collateral flow was probably not great. When the coronary artery stenosis was maintained after exercise, the abnormal distribution of myocardial blood flow across the ventricular wall was found to persist during the early post-exercise period. Thus, subendocardial perfusion remained depressed 1 min after exercise, and this was associated with substantially reduced regional mechanical performance at this time period. Persistent dysfunction early after exercise therefore appears to be dependent on persistent abnormalities of myocardial blood flow.

When the coronary artery stenosis was released immediately after exercise, patterns of regional myocardial blood flow and function in the early post-exercise period were quite different. Myocardial blood flow increased markedly at 1 min, probably reflecting both persistent increases in myocardial oxygen demand and reactive hyperemia. Regional function demonstrated a prompt return to the baseline value. Thereafter, however, regional function deteriorated rapidly, and by 5 min after cessation of exercise there were no differences in myocardial function for the persistent stenosis and temporary stenosis runs. Circumflex coronary artery flow remained somewhat elevated 5 min after exercise with temporary stenosis; thus, circumflex function and circumflex artery flow were dissociated at this time period. The total duration of dysfunction was ~15–30 min in this model, and was not dependent on the presence or absence of stenosis after exercise. This late component of post-exercise dysfunction is therefore a consequence of the myocardial ischemia that occurred during exercise, and is not related to persistent coronary artery stenosis. The possibility that subendocardial flow might have been reduced late following runs with temporary stenosis was not tested in this study. Smith (20) found decreased regional myocardial blood flow, oxygen consumption, and contractile function after release of 10-min coronary artery occlusions in anesthetized dogs, suggesting that post-ischemic dysfunction may be associated with decreased myocardial oxygen consumption and secondary decreases in blood flow. Thus, reductions in subendocardial flow late after exercise would be difficult to interpret, since this could be secondary to decreased oxygen consumption of post-ischemic myocardium.

The cause of late persistent dysfunction is unclear. This may be analogous to the persistent regional dysfunction that may occur following release of transient total coronary artery occlusions or prolonged partial occlusions (21) in resting dogs, a phenomenon termed "stunned" myocardium (22). In that model, prolonged depletion of high energy phosphates has been suggested as a possible explanation for this phenomenon (23–25). Alternatively, alterations in calcium flux (22), or possibly oxygen free radical associated damage (26), may be responsible.

The mechanism of the rebound in function that occurred early after exercise in the temporary stenosis group is also unclear; Pagani et al. (27) have noted similar responses following release of very brief total coronary artery occlusions in resting dogs. Beta-blockade and reserpine did not attenuate the rebound observed in that model, suggesting that this was not simply a manifestation of increased sympathetic stimulation. The current model differs in that substantial sympathetic tone was probably present in the early post-exercise period. Whether increased sympathetic nervous system activity may have contributed to the early transient recovery noted after the transient stenosis runs was not examined in this study. Also, in the study of Pagani et al., there was an actual overshoot such that function early after release of coronary artery occlusion transiently exceeded the baseline value, whereas in the current study only temporary return of function to the baseline value was observed before a subsequent deterioration. Tomoike et al. (28) also noted a transient partial improvement in regional function followed by a secondary deterioration in function after cessation of rapid atrial pacing in dogs with coronary artery stenoses. In that study, however, the coronary artery stenosis was maintained in the post-pacing period, whereas in the current study the transient recovery was noted only when the stenosis was released after exercise.

In this study, nonischemic segment shortening was significantly lower 15 min following runs with persistent stenosis compared with runs with temporary stenosis, although not different from resting control. This may partially reflect differences in ischemic segment shortening, which was greater (although not significantly) following persistent stenosis runs at this time period. Thus, there may have been less "compensatory" increase in distant segment shortening.

The severity of exercise-induced ischemia may vary with the precise mechanism of flow reduction, severity of flow restriction, degree of collateral flow, as well as exercise intensity and duration. Thus, the extent and duration of post-exercise dysfunction noted in this study may not be directly applicable to humans. Although the heart rates achieved during exercise in this study were far higher than those usually observed in exercising humans with coronary artery disease, they represent only ~80% of maximum canine heart rates. Robertson et al. (29) have noted regional wall motion abnormalities persisting up to 30 min after exercise in patients with coronary artery disease, indicating the potential clinical relevance of phenomena observed in this study.

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