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EXPERIMENTAL STUDIES

Quantitative Assessment of the Effects of a Fixed 50% Coronary Artery Stenosis on Regional Myocardial Flow Reserve and Transmural Distribution of Blood Flow

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Experimental coronary artery stenoses produced by external constrictors that reduce vessel diameter by 50% under basal conditions have been shown to reduce myocardial hyperemic flow reserve. Because such lesions may exhibit dynamic increases in severity during coronary vasodilation, the results of these studies are not necessarily applicable to human patients with fixed, proximal coronary stenoses of similar baseline severity. Accordingly, the present study was conducted in 16 closed chest conscious pigs in order to assess the effects of a fixed, rigid 50% stenosis on maximal myocardial hyperemic flow and transmural distribution of blood flow. Eight pigs (Group I, stenosis) were instrumented with a 50% stenosis and eight were not (Group II, control). After obtaining control measurements of hemodynamics and regional myocardial blood flow (microsphere technique), adenosine was infused at doses of 100, 200 and 400 $\mu g \cdot min^{-1}$ (× 10 minutes at each dose) directly into the left anterior descending coronary bed distal to the stenosis (Group I) or at a similar level in animals without a stenosis. Hemodynamics and blood flow measurements were made at the 10th minute of each infusion level of adenosine.

The results (mean ± 1 standard deviation) of the study were as follows. Under basal conditions, transmural, endocardial and epicardial flows ($ml \cdot min^{-1} \cdot g^{-1}$) in Group I pigs (1.48 ± 0.40, 1.51 ± 0.45 and 1.30 ± 0.35, respectively) did not differ significantly from respective flows in Group II pigs (1.56 ± 0.26, 1.57 ± 0.27 and 1.43 ± 0.30). Likewise baseline endocardial to epicardial flow ratios were comparable between the two groups (Group I = 1.16 ± 0.22 versus Group II = 1.11 ± 0.09, p = NS). Transmural, endocardial and epicardial blood flow in Group I pigs increased to the same extent as respective flows in Group II pigs at each dose of adenosine tested. Maximal transmural, endocardial and epicardial flows in Group I pigs increased, respectively, to levels 3.56 ± 1.56, 3.56 ± 2.03 and 3.26 ± 1.16 above baseline values. Similar responses occurred in Group II (3.38 ± 1.02, 3.21 ± 0.91 and 3.25 ± 1.44, respectively). The endocardial/epicardial flow ratio in Group I at maximal vasodilation (1.20 ± 0.34) did not differ significantly from that in Group II (1.19 ± 0.34). Thus, the data demonstrate that in contrast to 50% stenoses formed with external coronary constrictors, fixed proximal 50% stenoses do not reduce maximal myocardial hyperemic flow reserve.

The extent to which maximal myocardial hyperemic flow reserve is reduced by a fixed proximal coronary artery stenosis that reduces vessel diameter by 50% is uncertain. Although data from canine experiments indicate that 50% stenoses produced with external coronary artery constrictors reduce myocardial flow reserve (1–3), these observations may not be entirely applicable to human patients with fixed, calcified coronary stenoses of only modest severity. This is true because coronary vasodilation in the setting of a nonrigid coronary stenosis may result in dynamic alterations in stenosis geometry (for example, collapse of the vessel at the site of the lesion) which in turn may increase the hemodynamic severity of the lesion (4–8). Furthermore, there are no data available concerning the influence of a fixed, proximal 50% stenosis on the transmural distribution of blood flow under conditions of maximal vasodilation. In light of these considerations, the present investigation was undertaken in order to: 1) characterize the influence of a fixed, proximal 50% coronary artery stenosis on myocardial flow reserve, and 2) determine quantitatively the influence of such a lesion on the transmural distribution of blood flow both at rest and in response to coronary vasodilation. Studies were performed in two groups of conscious pigs, one with and one without a rigid artificial coronary artery stenosis that reduced vessel diameter by 50%.

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Methods

Animal Preparation

Farm-bred pigs (n = 16; mean weight 48.0 kg; range 38.4 to 58.6) were prepared for the study in the following way. The animals were anesthesized with halothane (0.5 to 1.5%) and nitrous oxide, and intubated and ventilated with a volume cycled respirator. Cutdowns were made over both groins and the right carotid artery. The animal was then heparinized (225 IU·kg^{-1}) after which an 8 F double lumen catheter was inserted into the left femoral artery and advanced to the thoracic aorta. This line was used to monitor pressure, obtain samples of blood for pH, P_{O_2} and P_{CO_2} and to withdraw blood for determination of regional myocardial blood flow with radioactive microspheres (9). The right femoral artery was used for insertion of an 8 F angiographic catheter. The catheter was advanced under fluoroscopic control to the left ventricle and then retrograde across the mitral valve into the left atrium. This catheter was used for the injection of radioactive microspheres. An 8 F double lumen catheter was inserted into the left femoral vein and advanced to the inferior vena cava; this catheter was used for infusion of fluids (Ringer's lactate) and drugs during the study.

Group I (50% stenosis). In eight of the animals an 8 French Amplatz catheter was inserted into the right carotid artery and advanced under fluoroscopic control to the left anterior descending coronary artery. The artery was visualized by hand injection of 3 to 5 cc Renografin-76 after which a 0.018 Teflon-coated guidewire with a 3 cm floppy distal end was inserted into the vessel. The Amplatz catheter was removed and a plastic stenosis (7.0 mm long; outer diameter 3.6 mm, diameter inner 1.8 mm) with an eccentric lumen advanced over the wire into the proximal one-third of the coronary artery. The wire was quickly removed leaving the stenosis in place (Fig. 1). The stenosis contained a second lumen into which the distal end of a 1.0 mm diameter, 70 cm long plastic catheter had been attached before placement of the stenosis. The distal end of the catheter was open to the distal end of the stenosis and was used to record pressure from and infuse adenosine into the portion of the left anterior descending coronary artery distal to the stenosis. The method for inserting the stenosis and the frequency response of the catheter used to record distal coronary pressure have been described previously (10,11). The rigid nature of the device coupled with the extremely flexible nature of the guidewire and "pushing" catheter used to insert it assured that the stenosis always came to rest at a point in the coronary artery whose diameter matched the external diameter of the stenosis itself (that is, 3.6 mm). It is not possible to advance the device into a portion of the vessel substantially narrower than that of the external diameter of the stenosis.

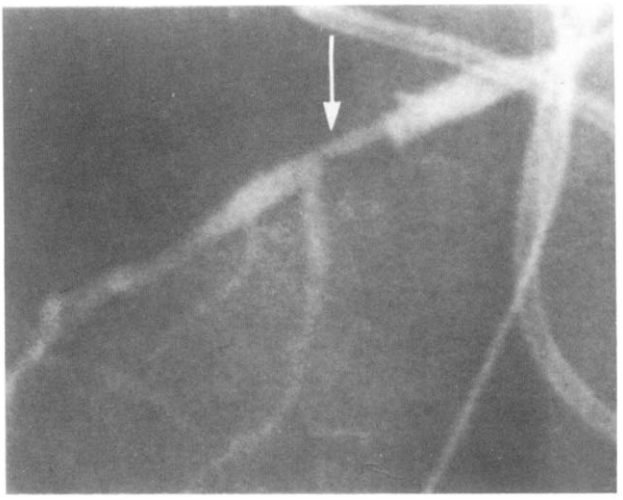

Figure 1. A selected frame obtained from a coronary angiogram of one pig used in the study. The **arrow** points to the narrowing in the vessel produced by the artificial stenosis. Note that the lesion produced is: 1) a relatively long one from a clinical point of view, and 2) eccentric owing to the presence of a second lumen within the device (see Methods). Comparison of the diameter of the stenosed coronary segment (1.8 mm by definition) with the nonstenosed area proximal to it clearly illustrates that luminal diameter of the vessel has been reduced by 50%. The X-ray image was recorded on 35 mm Kodak CFX film with the aid of a 6 inch (15.2 cm) cesium iodide image intensifier capable of resolving 1.5 to 2.0 line pairs/mm (10).

Group II (control). In the remaining eight pigs, only the 1.0 mm diameter pressure/infusion catheter was inserted into the animal's left anterior descending coronary artery (proximal one-third). The catheter was introduced into the artery by passing it through the Amplatz catheter. The Amplatz catheter was then withdrawn leaving the infusion catheter in place.

Measurements. The animals' heart rate (electrocardiographic lead II) was monitored continuously throughout the study. All pressures were obtained with Hewlett-Packard pressure transducers (Model 1280) and recorded on paper with a Hewlett-Packard recorder (Model 8877) for subsequent analysis. It should be noted that the transducers used to record pressure proximal and distal to the stenosis were held in the same stand, level with the animal's mid-right atrium. The transducers were balanced and calibrated identically as evidenced by the fact that identical pressures were recorded from the same source when the catheters were switched from one transducer to the other.

After instrumentation had been accomplished, all cutdown sites were closed. After emergence from anesthesia, small doses (20 to 40 mg) of sodium thiamylal were given intravenously throughout the study in order to ensure that the animal was comfortable and rested quietly. Although sedated, the animals breathed spontaneously, were awake and had brisk corneal reflexes.

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Experimental Protocol

On the day of the study each animal was given aspirin (150 mg intravenously) to prevent platelet aggregation within the lumen of the stenosis (12). Group II animals also were given the same dose of aspirin even though they were not instrumented with the stenosis. After the animals' condition had stabilized for approximately 20 to 30 minutes, control measurements of hemodynamics and regional myocardial blood flow were obtained with the animal lying quietly on its side. Next, adenosine was given directly into the left anterior descending coronary bed distal to the stenosis (Group I). Adenosine was infused in a constant volume (0.123 $ml \cdot min^{-1}$) with concentration adjusted to deliver 100, 200 and 400 $\mu g \cdot min^{-1}$. Each infusion was maintained for 10 minutes at which time repeat measurements of hemodynamics and blood flow were made. It should be noted that the infusion lines were first cleared and then flushed with a normal saline solution and 10 minutes allowed to elapse before infusion at the next higher dose level began. Control measurements were made while normal saline solution was infused into the distal coronary circulation at the same rate used to infuse adenosine. After completion of the last adenosine infusion, marker microspheres were injected into the perfusion catheter in order to objectively demarcate myocardium that had been exposed to the adenosine infusion. Approximately 300,000 microspheres (15 μ diameter, total activity/injection 2 to 4 μCi) were used for this purpose. After injection of the marker microspheres, the animal was given a large intravenous dose of sodium thiamylal (200 to 300 mg) and then 3 to 4 minutes later was sacrificed by injecting potassium chloride into the left atrium. Group II animals were studied according to the same protocol save for the fact that an artificial stenosis was not employed.

Determination of Regional Myocardial Blood Flow

For each experimental condition approximately 4×10^6 radiolabeled microspheres (15μ diameter, 85 to 105 μCi total radioactivity) were injected through the left atrial catheter. A precisely timed, 2 minute reference collection of arterial blood began 15 to 30 seconds before injection of the radiolabeled microspheres. Blood was withdrawn at a constant rate (10 ml/min) from the thoracic aortic catheter into a 50 ml pre-weighed glass syringe by means of a Harvard pump. It should be noted that: 1) a different radioisotope was chosen at random for each flow determination, and 2) the microspheres were suspended in 10% dextran with 0.01% Tween-80 and sonically dispersed for 15 minutes before each injection.

Ventricular tissue samples. After sacrifice, the heart was removed and sectioned for determination of microsphere activity. The free wall of the left ventricle was removed from the heart after which epicardial blood vessels and fat were carefully trimmed away. Next, the ventricle was cut into cubes weighing 1 to 3 g and the location of each carefully noted on a diagram of the free wall of the ventricle. Each cube was divided into endocardial and epicardial halves, and then divided into quarters, to obtain endocardial and epicardial layers that represented, respectively, the innermost and outermost quarter of the left ventricular wall. Each quarter of the transmural cube weighed between 0.25 and 0.75 g. The samples were placed in a pre-weighed plastic vial, after which the vials were weighed again and then counted in a gamma well counter (Packard Instruments). A computer was used to correct for spillover of counts from 1 isotope into the window of another and to calculate regional myocardial blood flow ($ml \cdot min^{-1} \cdot g^{-1}$) in each tissue sample.

Analysis of tissue samples. For purposes of this analysis only tissue samples from the free wall of the left ventricle in the distribution of the left anterior descending coronary artery that received the drug infusion were analyzed. These samples were readily identified because each contained a high concentration ($\geq 7{,}000 \cdot g^{-1}$) of marker microspheres. Flow results in endocardial and epicardial layers of each zone are based on data obtained from the innermost and outermost quarters of the myocardial wall, respectively; transmural flow results, however, are based on activity of each isotope in all four quarters of each transmural cube. The value of transmural flow for each cube represents a weighted mean average of calculated flows for each of the four quarters constituting the cube.

Tissue samples that exhibited control flows of 2 or more standard deviations below mean flow for the zone distal to the stenosis (distal zone) were considered to be severely ischemic and thus were excluded from analysis. Such samples were always perfused by a small diagonal branch of the left anterior descending coronary artery which in some experiments had been occluded by the stenosis at the point at which it came to rest in the main vessel. Because the purpose of this study was to examine hyperemic reserve distal to a mildly stenosed coronary artery, tissue specimens whose blood supply had been completely occluded by the walls of the stenosis were excluded from analysis.

Statistical Methods

The significance of group mean changes (versus control) in hemodynamic variables and regional myocardial blood flow in response to each dose of adenosine were assessed by means of blocked one-way analysis of variance and Dunnett's test (13). This approach also was used to compare Group I with Group II flow responses to adenosine infusion. Blocked one-way analysis of variance permitted the effects of animal to animal variability to be separated from treatment effects attributable to the stenosis. This provided a sensitive statistical tool for detecting potential differences

in group mean flow responses to adenosine. Indeed, because only two groups were compared, this method of analysis is equivalent to a paired *t* test. Results were considered statistically significant when $p < 0.05$. All values are expressed as mean ± standard deviation.

Results

Hemodynamics (Table 1)

Heart rate, mean aortic and mean left atrial pressures did not change significantly from control values at any level of adenosine infusion in Group II (control) animals. Similarly, for Group I (stenosis) animals heart rate and mean left atrial pressure did not change significantly from control values at any dose of adenosine infusion. Mean aortic pressure increased modestly but significantly versus control at adenosine doses of 100, 200 and 400 $\mu g \cdot min^{-1}$. The mean pressure gradient across the stenosis also increased significantly versus control at the 200 and 400 $\mu \cdot min^{-1}$ doses. Although the mean value also increased at the 100 $\mu g \cdot min^{-1}$ dose, the change in mean pressure gradient failed to attain statistical significance.

Regional Myocardial Blood Flow (Table 2 and Fig. 2)

Under basal conditions transmural, endocardial and epicardial blood flow distal to the stenosis did not differ significantly from respective flows in the left anterior descending coronary bed of the control animals. Likewise, control endocardial to epicardial flow ratios did not differ significantly between the two groups. In both groups regional endocardial and transmural blood flow increased significantly versus control levels of adenosine infusion. Regional epicardial blood flow distal to the stenosis also increased significantly versus control with each dose of adenosine. Epicardial blood flow in control animals failed to increase significantly versus control with the 100 $\mu g \cdot min^{-1}$ adenosine dose, but did increase significantly at both the 200 and 400 $\mu g \cdot min^{-1}$ doses. Finally, the endocardial to epicardial flow ratio did not change significantly from control values in either group of animals at any level of adenosine infusion.

Comparison (Group I vs. Group II) of transmural, endocardial and epicardial flow responses to each level of adenosine infusion yielded the following results (Table 3 and Fig. 2): The relative increase over control levels in endocardial, epicardial and transmural blood flow distal to the stenosis did not differ significantly in comparison with flow increases in the unobstructed left anterior descending bed at any dose of adenosine infusion. Analysis of the data on an animal by animal basis also demonstrated that epicardial and transmural flow responses were very similar for the two groups. Endocardial flow responses to adenosine, however, were more variable. At the highest dose of adenosine infusion, endocardial flow for seven of eight control animals was greater than or equal to 2.5 times rest levels. In contrast at the 400 $\mu g \cdot min^{-1}$ dose, four animals in the stenosis group manifested endocardial flow increases that clustered between 2.0 and 2.5 times rest levels, while three animals increased endocardial flow between five and seven times rest levels. The reason for this variability is unclear although a comparable degree of variation in the maximal endocardial flow response to a hyperemic stimulus has been reported by others in laboratory animals with unobstructed coronary arteries (14,15).

Discussion

Fixed coronary stenoses and myocardial blood flow. Our results confirm certain observations made in ear-

Table 1. Hemodynamic Data (mean ± 1 standard deviation)

		Adenosine (intracoronary) ($\mu g \cdot min^{-1}$)		
	Control	100	200	400
Group I (50% stenosis group; n = 8)				
Heart rate (min^{-1})	82 ± 20	82 ± 29	77 ± 16	87 ± 21
Aortic mean pressure (mm Hg)	118.0 ± 14.7	125.0 ± 15.4*	127.0 ± 16.7*	127.0 ± 15.6*
Distal coronary mean pressure (mm Hg)	114.0 ± 14.9	117.0 ± 13.3	116.0 ± 14.0	106.0 ± 14.2*
Stenosis gradient (mm Hg)	3.8 ± 2.1	7.6 ± 4.0	10.9 ± 4.5†	20.6 ± 8.9†
Left atrial mean pressure (mm Hg)	4.0 ± 2.7	3.6 ± 2.3	4.3 ± 3.2	3.5 ± 4.5
Group II (control; n = 8)				
Heart rate (min^{-1})	91 ± 12	88 ± 13	91 ± 12	95 ± 14
Aortic mean pressure (mm Hg)	121.0 ± 9.8	125.0 ± 13.4	125.0 ± 12.7	124.0 ± 11.6
Left atrial mean pressure (mm Hg)	3.6 ± 1.8	4.1 ± 1.1	4.3 ± 2.4	4.9 ± 1.1

*$p < 0.05$ versus control; †$p < 0.01$ versus control.

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Table 2. Regional Myocardial Blood Flow (ml·min^{-1}·g^{-1}; mean ± 1 standard deviation)

	Control	Adenosine (intracoronary) (μg·min^{-1})		
		100	200	400
Group I (50% stenosis)				
Transmural	1.48 ± 0.40	2.69 ± 0.75†	3.51 ± 0.95†	4.86 ± 1.32†
Endocardial	1.51 ± 0.45	2.68 ± 0.67*	3.45 ± 0.95†	4.72 ± 1.67†
Epicardial	1.30 ± 0.35	2.31 ± 0.71†	2.85 ± 0.77†	3.99 ± 0.95†
Endocardial/epicardial ratio	1.16 ± 0.22	1.19 ± 0.19	1 22 ± 0.17	1.20 ± 0.34
Group II (control)				
Transmural	1.56 ± 0.26	2.43 ± 0.53†	3.67 ± 0.93†	5.11 ± 1.17†
Endocardial	1.57 ± 0.27	2.53 ± 0.82†	3.62 ± 1.02†	4 86 ± 0 80†
Epicardial	1.43 ± 0.30	2.10 ± 0.48	3.16 ± 0.99†	4.44 ± 1.63†
Endocardial/epicardial ratio	1.11 ± 0.09	1.22 ± 0.33	1.20 ± 0.28	1.19 ± 0 34

* $p < 0.05$ versus control, † $p < 0.01$ versus control

lier studies employing canine preparations instrumented with external coronary artery constrictors that reduced vessel diameter by 50% (1–3). Thus, we found that a fixed, proximal 50% coronary stenosis does not reduce myocardial blood flow under basal conditions. Our data also demonstrate in a quantitative fashion that such a stenosis does not alter the normal resting transmural distribution of blood flow. However, in contrast to previous investigations (1–3) our results indicate that a fixed, proximal 50% stenosis does not impair the hyperemic flow response to a maximal, pharmacologic vasodilatory stimulus. This was true for both the epicardial and the endocardial flow response to adenosine. Accordingly, the endocardial to epicardial flow ratio in myocardium distal to the stenosis also did not change versus control during maximal vasodilation.

The fact that a maximal flow response was attained with the highest dose of adenosine employed in this study is supported by the absolute levels of myocardial blood flow achieved for both groups of animals (Table 2). The group mean values of maximal flow observed in our experiments are very similar to those reported by other investigators (14,15). Somewhat higher values of rest myocardial blood

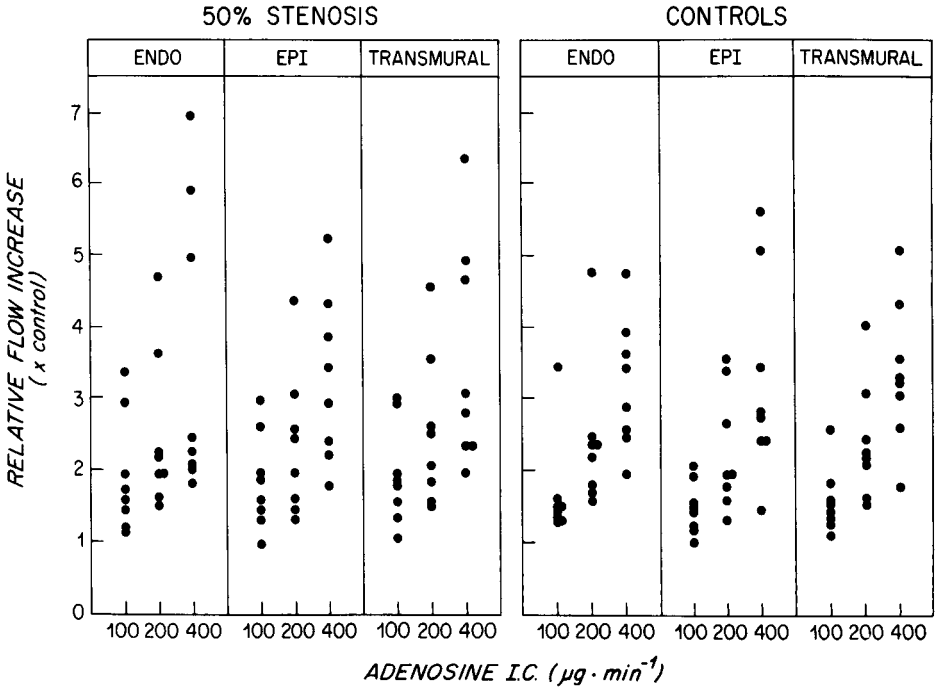

Figure 2. Endocardial (ENDO), epicardial (EPI) and transmural blood flow responses to intracoronary (I.C.) adenosine infusion for each of the 16 pigs in the study. Flow responses are expressed as relative increase times (X) control. Group mean values for absolute levels of regional myocardial blood flow at each dose of adenosine infused are given in Table 2. Note that the flow responses are much the same for both groups of pigs.

Table 3. Regional Myocardial Blood Flow: Relative Increase Times Control (mean ± 1 standard deviation)

	Adenosine (intracoronary) ($\mu g \cdot min^{-1}$)								
	100			200			400		
	ENDO	EPI	TM	ENDO	EPI	TM	ENDO	EPI	TM
Group I	1.93 ± 0.80	1.85 ± 0.67	1.92 ± 0 71	2.48 ± 1 11	2 35 ± 0.99	2.53 ± 2.03	3.56 ± 1.56	3.26 ± 1.16	3.56 ± 1.56
Group II	1.67 ± 0.74	1.50 ± 0.35	1.60 ± 0 47	2.41 ± 1.02	2.29 ± 0.84	2.42 ± 0.81	3.21 ± 0.91	3.25 ± 1.44	3.38 ± 1.02

ENDO = endocardial; EPI = epicardial; TM = transmural

flow in our animals, however, could have been related to a combination of factors including instrumentation with resulting stress and hypertension.

Failure of endocardial to epicardial flow ratios to change significantly (vs. basal levels) in response to maximal coronary vasodilation has been reported by others in animals with unobstructed coronary vessels both in response to intracoronary adenosine infusion (14) and during reactive hyperemia after release of a 45 second coronary occlusion (15). Although we cannot exclude systemic hypertension (present in our animals as well as those of Wartlier et al. [14]) as a contributing factor in maintaining normal endocardial to epicardial flow ratios during maximal coronary vasodilation, hypertension may not be required because the animals reported by Fedor et al. (15) were normotensive.

Factors affecting the pressure gradient across the coronary stenosis. The role played by arterial hypertension in causing transmural flow to increase to a comparable extent in response to adenosine in stenosis animals versus control animals also must be considered. Elevation of arterial pressure has been shown to increase total reactive hyperemic blood flow in canine preparations with unobstructed coronary arteries (16). At the 400 $\mu g \cdot min^{-1}$ dose of adenosine, a mean pressure gradient of 20.6 ± 8.9 mm Hg developed across the stenosis (Table 1). This pressure loss is obligatory, incurred as a result of energy dissipated in the form of friction and turbulence plus that stored in momentum due to acceleration of blood. Elevation of mean aortic pressure would permit a higher mean distal coronary pressure to be maintained at any given flow rate and therefore could have contributed to the attainment of maximal myocardial flows in animals with coronary stenosis that were comparable with those seen in control animals.

However, maintenance of maximal flow rates in the stenosis group comparable with those of the control group, despite lower mean coronary perfusion pressure in the former, does not necessarily indicate that distal coronary arteriolar resistance was lower in the stenosis group. Although some of the potential energy (that is, proximal aortic pressure) used in moving blood across the stenosis is required to overcome the effects of friction and turbulence, some is also stored in the form of momentum resulting from acceleration of blood (7,17). For arterial narrowings that reduce vessel diameter by less than 80%, acceleration of blood probably contributes most to pressure losses across a stenosis (17). Thus, because much of the pressure (that is, potential energy) "lost" in transfering blood across the stenosis is converted to a form (that is, momentum) which promotes movement of blood through the distal coronary bed, at least partial compensation is made for the reduction in static pressure at the distal end of the stenosis. Furthermore, in our study the pressure gradient measured across the stenosis may have been exaggerated because distal pressure was measured precisely at the point where the column of blood emerged from the device. Flow velocity is highest and therefore pressure is lowest at this point. Nevertheless, we cannot exclude the possibility that distal arteriolar tone in stenosis animals may have been somewhat reduced in comparison with control animals. A reduction in arteriolar tone caused by a relative reduction in intravascular pressure distal to the stenosis (myogenic reflex [18]) may have occurred and could have rendered these vessels more sensitive to any given dose of adenosine. Such a mechanism could be operative under physiologic conditions and thus could partially help to account for failure of a fixed, proximal 50% stenosis to limit maximal myocardial flow.

Role of systemic hypertension. In any event the presence of modest systemic hypertension in our animals does not diminish the relevance of these observations to normotensive human subjects with fixed 50% coronary stenoses. Elevation of systemic arterial pressure to levels comparable with those seen in the present study is common in normotensive patients during moderate to heavy physical exertion (19), precisely the circumstances in which a relative flow deficit could be expected. Thus, systemic hypertension demonstrated in our animals does not negate the relevance of this study to normotensive patients with fixed 50% coronary stenoses.

Factors related to the diameter and length of the stenosis. The coronary perfusion catheter (1 mm diameter) reduced the luminal diameter of the control animal's left anterior descending coronary artery by roughly 25%; this factor also should be addressed. It is unlikely that this can account for comparable maximal flow responses observed in stenosis versus control animals, because previous authors (1,2) have shown that stenoses that reduce vessel diameter by 25% have no effect on myocardial hyperemic flow reserve. Thus, the presence of the perfusion catheter in the

control animals is unlikely to have spuriously influenced the results of the study.

The length of the stenosis (20), its absolute diameter and the size of the arterial lumen in which it rests all can influence its hemodynamic severity (21). If severity is defined as the pressure gradient ($\triangle$ P) required to achieve a given flow *velocity* ($cm \cdot s^{-1}$) in a normal segment of vessel just proximal to the stenosis, then it can be shown that the principal determinant of $\triangle$ P is the relative diameter reduction of the normal vessel caused by the stenosis (21). Stenoses of unequal absolute diameters that produce identical percent reductions in luminal diameter have identical gradient/flow velocity plots (21). On the other hand, stenoses of equal absolute diameters that cause different percent reductions of vessel diameter yield very different gradient/flow velocity relations. In contrast, if severity is assessed by plotting $\triangle$ P as a function of volume flow ($ml \cdot s^{-1}$), then the opposite is true. Stenoses of the same absolute diameter have nearly identical gradient/volume flow relations regardless of the percent reduction in luminal diameter that they produce (21). Likewise, stenoses of unequal absolute diameter exhibit different gradient/volume flow relations even when they produce identical percent reductions in vessel diameter (21).

Stenosis severity versus gradient/volume flow relations. Because the present study is primarily concerned with relative flow changes permitted by a fixed stenosis in response to coronary vasodilation, it is appropriate to consider stenosis severity in terms of gradient/volume flow relations (21). Viewed in this context, at any given flow rate the absolute diameter of the stenosis becomes the principal determinant of its hemodynamic severity. On the basis of fluid dynamic principles, the diameter of the lesion employed in this study would be expected to cause only modest pressure gradients even at high flow rates (21). Mean gradients measured at maximal flows in the animals reported here support this view. Nevertheless, because coronary arteries in human beings have proximal luminal diameters that range between 3.0 and 4.0 mm (22), it is apparent that the size of the artificial stenosis employed in this study is relevant to patients with rigid, proximal 50% lesions. More distal 50% stenoses would, of course, have smaller absolute diameters and, therefore, would be expected to exhibit steeper gradient/volume flow relations (that is, larger gradient for a given volume flow). Accordingly, it is possible that more distal 50% stenoses might reduce maximal levels of myocardial blood flow, although the impact of this in terms of overall ventricular function may be less. Nevertheless, such distal lesions conceivably could cause symptoms and perhaps even signs of myocardial ischemia.

Length versus cross-sectional area of a coronary stenosis. As mentioned, length as well as cross-sectional area of a coronary stenosis may influence its effects on coronary flow reserve (3,20). In an earlier study (3), it was demonstrated that 50% stenoses 5 mm or more in length reduce peak reactive hyperemic flow between 30 and 50%. These results contrast sharply with those obtained in the present study in which a 7 mm long fixed, rigid stenosis was employed. It seems unlikely that the design of the present study in which one group of animals with a stenosis was compared with a second group without a stenosis can explain these differences because: 1) in our study the two groups were closely matched with respect to hemodynamics and myocardial blood flow under control conditions, and 2) animal to animal variability in terms of myocardial blood flow response to adenosine was controlled in the statistical analysis of the data. Furthermore, flow increases obtained in our study (3 to 3.5 times levels at rest) were comparable with those observed in an earlier investigation (3). Accordingly, it is likely that some other factor is responsible for the differences observed. A dynamic increase in stenosis severity secondary to coronary vasodilation is a plausible explanation. However, other differences in experimental models employed (for example, species, anesthesia, basal levels of flow and absolute stenosis dimensions) might have contributed to these disparate results.

In any case, because the artificial stenosis employed in this study represents a relatively long lesion from a clinical point of view (Fig. 1), it is likely that the results obtained approach a "worst case" estimate for the effects of a fixed, isolated, proximal 50% stenosis on myocardial flow reserve. Nevertheless, it is possible if a fixed, proximal 50% lesion were considerably longer or if several short 50% lesions occurred in series that hyperemic flow reserve might be adversely affected. Similarly, we cannot exclude the possibility that certain other extreme conditions (for example, left ventricular hypertrophy with tachycardia and hypotension) also could result in a perfusion deficit distal to a fixed, 50% stenosis.

Clinical implications. Finally, it also should be noted that although many patients with coronary artery disease undoubtedly have stenoses that may change in severity in response to various interventions (23,24) this fact does not negate the observation that there are others who have fixed lesions. Of 50 individual stenoses that reduced vessel diameter 30 to 70% reported by Brown et al. (23), more than half (27 of 50) failed to exhibit a statistically significant change in stenosis flow resistance in response to nitroglycerin. This observation supports the notion that many coronary stenoses of mild to moderate severity may be rigid in nature. Because coronary pressure/flow relations under conditions of coronary vasodilation may be different for fixed versus dynamic lesions, it is logical that they be considered separately notwithstanding the fact that both may exhibit similar degrees of luminal narrowing under basal conditions. The present study was designed to better understand the effects of a fixed, proximal 50% stenosis on myocardial flow reserve. Accordingly, we believe the model employed is appropriate for this purpose and is relevant to a substantial percentage (perhaps as many as 50%) of clinically encoun-

tered coronary lesions of similar location and severity. The data obtained indicate that *fixed, proximal* 50% stenoses are: 1) unlikely to limit myocardial flow reserve; 2) do not alter the normal transmural distribution of myocardial blood flow either at rest or during pharmacologic coronary vasodilation, and therefore are 3) unlikely to cause signs or symptoms of myocardial ischemia.

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References

1. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and region distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol 1974;33.87–94
2. Gould KL. Assessment of coronary stenoses with myocardial perfusion imaging during pharmacologic coronary vasodilation. IV. Limits of detection of stenosis with idealized cross-sectional imaging system. Am J Cardiol 1978;42:761–8
3. Feldman RL, Nichols WW, Pepine CJ, Conetta DA, Conti CR The coronary hemodynamics of left main and branch coronary stenosis. The effects of reduction in stenosis diameter, stenosis length and number of stenoses. J Thorac Cardiovasc Surg 1979,77:377–88
4. Schwartz JS, Carlyle PF, Cohn JN. Effect of dilation of the distal coronary bed on flow and resistance in severely stenotic coronary arteries in the dog Am J Cardiol 1979;43:219–24.
5. Schwartz JS, Carlyle PF, Cohn JN Effect of coronary arterial pressure on coronary stenosis resistance Circulation 1980;61:70–6.
6. Gould KL Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. Circ Res 1978;43:242–53.
7 Gould KL, Kelley KO. Physiological significance of coronary flow velocity and changes in stenosis geometry during coronary vasodilation in awake dogs. Circ Res 1982;50:695–704
8. Gould KL. Collapsing coronary stenosis—a Starling resistor (editorial). Int J Cardiol 1982;2:39–42
9. Domenich RJ, Hoffman JIE, Nobel MIN, Saunders KB, Henson JR, Subijanto S. Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs. Circ Res 1969;25:581–96.
10. Gewirtz H, Most AS. Production of a critical coronary arterial stenosis in closed chest laboratory animals Description of a new non-surgical method based on standard cardiac catheterization techniques. Am J Cardiol 1981,47·589–96.
11. Gewirtz H, Most AS, Williams DO The effect of generalized alpha receptor stimulation on regional myocardial blood flow distal to a severe coronary artery stenosis. Circulation 1982;65:1329–36.
12. Folts JD, Crowell EJ Jr, Rowe GG. Platelet aggregation in partially obstructed vessels and its elimination with aspirin. Circulation 1975,54:365–70.
13. Winer BJ. Statistical Principles in Experimental Design 2nd ed New York: McGraw-Hill, 1971.201–4
14. Warltier DC, Gross GJ, Brooks HL Pharmacologic-vs-ischemia induced coronary artery vasodilation. Am J Physiol (Heart Circ Physiol) 1981,9:H767–74
15 Fedor JM, McIntosh DM, Rembert JC, Greenfield JC Jr. Coronary and transmural myocardial blood flow responses in awake domestic pigs. Am J Physiol (Heart Circ Physiol) 1978:H435–44
16 Dole WP, Montville WJ, Bishop VS. Dependency of myocardial reactive hyperemia on coronary artery pressure in the dog Am J Physiol (Heart Circ Physiol) 1981;9:H709–15.
17 Young DF, Cholvin NR, Roth AC. Pressure drop across artificially induced stenoses in the femoral arteries of dogs. Circ Res 1975,36:735–43.
18. Giles RW, Wilcken DL. Reactive hyperemia in the dog heart: evidence for a myogenic contribution. Cardiovasc Res 1977,11:64–73
19. Barnard RJ, MacAlpin R, Kattus AA, Buckberg GD. Ischemic response to sudden strenuous exercise in healthy men Circulation 1973;48:936–42.
20. Feldman RL, Nichols WW, Pepine CJ, Conti CR. Hemodynamic significance of the length of a coronary arterial narrowing. Am J Cardiol 1978;41.865–71.
21. Gould KL: Dynamic coronary stenosis (special commentary). Am J Cardiol 1980;45:286–92.
22 Gensini G. Coronary arteriography In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine Philadelphia. WB Saunders, 1980:315.
23. Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HT. The mechanisms of nitroglycerin action: stenosis vasodilation as a major component of the drug response. Circulation 1981,64:1089–97.
24. Brown BG, Josephson MA, Petersen RB, et al. Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in coronary flow in patients with coronary artery disease. Am J Cardiol 1981;48·1077–85