Compensatory Changes of the Distal Coronary Vascular Bed During Progressive Coronary Constriction

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SUMMARY
The degree and effectiveness of compensatory changes in the distal coronary vascular bed during progressive proximal coronary stenosis have not been described. In this study, coronary vascular bed resistance and pressure gradient-flow relationships were determined for 157 different stenoses in nine opened-chest dogs by measuring coronary flow, aortic pressure, and coronary pressure distal to a coronary constrictor while flow was varied from resting to maximal values by the intracoronary injection of Hypaque-M, 75% (previously shown to cause transient, maximal vasodilatation comparable to ten second occlusion). This approach provided a means of hemodynamically characterizing coronary stenoses in a standard, experimental manner for quantitative analysis of different arteries at different flow rates as found in the intact coronary circulation. The results show that 1) pressure gradient-flow characteristics or hydraulic resistance of stenoses do not become abnormal enough to alter normal resting coronary flow nor to elicit compensatory changes for stenoses up to constriction of approximately 60% of the diameter, 2) compensatory vasodilatation of the distal coronary vascular bed maintains near normal resting flow for lesions between 60% and 85% diameter stenosis but adaptive vasodilatation fails to compensate for the high resistance of lesions greater than 85% diameter stenosis, and 3) there is vasodilator reserve still present when total coronary artery flow is reduced below normal by a stenosis. This vasodilator reserve probably exists in the epicardium since the endocardium is characteristically underperfused due to the low coronary pressure caused by stenosis and is therefore likely to be maximally vasodilated with no remaining vasodilator reserve.

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Intracoronary pressure
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Coronary stenosis
Coronary blood flow
Hemodynamics
Atherosclerosis

RESTING CORONARY FLOW and regional distribution remain normal despite relatively severe narrowing of a coronary artery.1,2 This has been explained in two ways. The first explanation emphasizes nonbiologic, hydraulic characteristics of the stenosis to explain normal flow despite luminal narrowing, and particularly the relation between stenosis radius and resistance as expressed by Poiseuille’s equation.6,7 The second emphasizes the compensatory or autoregulative changes occurring in the distal coronary vascular bed as proximal stenosis develops.3,8,9 This study examines the relative importance and interrelationship of these two mechanisms in the intact coronary circulation.

Methods
Nine black Labrador or German Shepherd dogs with mean body weights of 28 ± 8 kg were studied. Pentobarbital anesthesia was induced one hour after 30–45 mg of subcutaneous morphine sulfate. Respirations were controlled with a Harvard ventilatory pump through a cuffed endotracheal tube. Respiratory volumes were monitored with a Draeger volumeter and blood gases maintained normal by volume adjustment and supplemental oxygen. The left circumflex coronary artery was isolated through a left thoracotomy and external diameter of the proximal circumflex measured with calipers. An appropriately-sized, perivascular electromagnetic flow transducer (Zepeda) was implanted. A variable snare type occluder was placed distal to the flow transducer. It consisted of a 2–3 mm wide band of umbilical tape passed around the artery, through a stiff tubing, and attached to a machinist’s micrometer. The snare could be closed by small precise amounts according to the 0.01 mm micrometer scale. Approximately one centimeter distal to the constrictor, a small (one millimeter outside diameter by 1.5 inches long), teflon, end-hole catheter (Bardic 1968-T) was inserted two millimeters into the coronary lumen. This catheter is hereafter called the circumflex catheter and was used for injecting contrast media and recording coronary pressure distal to the constrictor.

Neither the flow transducer nor circumflex catheters affected maximum coronary flows or induced significant pressure gradients. This observation was repeatedly confirmed by recording maximal flows before and after insertion of the circumflex catheters and by recording circumflex coronary pressure during hyperemia before and after removal
of the flow transducer. In four dogs a Sones coronary arteriography catheter was inserted through the left carotid artery and positioned at the ostium of the left coronary artery. Withdrawal of this catheter did not change either resting or maximal hyperemic flows. After withdrawal to exclude possible effects of this catheter on flow, the catheter was replaced in the same position for the duration of the experiment for purposes of injecting contrast media. A 30 cm, 8 French teflon catheter was positioned at the base of the aorta through the right carotid artery in all dogs.

All data were recorded on an Electronics for Medicine DR-12 recorder at paper speeds from 25 to 100 mm per second. Pressures were measured in the aorta with a Statham P-23Db transducer and in the circumflex catheters with solid state, microdisplacement Kulite PSL 125-6 transducers, all of which were matched before, during, and after each experiment. Circumflex coronary flow was measured with a Zepeka, square wave, electromagnetic flowmeter operating at 400 Hz with flow transducers calibrated in vitro by graduated cylinder and stopwatch.

Occlusive zero at the beginning corresponded to occlusive zero at the end of each study. Pressures and flows were recorded in phasic and mean mode simultaneously. A limb lead electrocardiogram was monitored.

Experimental procedure was as follows. All dogs were heparinized intravenously. Baseline resting flow was recorded; the circumflex artery was gently occluded with forceps for 10 seconds and the hyperemic response recorded. The circumflex catheters were then inserted and reactive hyperemia to 10 second occlusion was repeated in order to verify that these catheters did not impair flow responses. Coronary flow, aortic pressure, and coronary pressure distal to the constrictor were then recorded throughout the experiment. Contrast media (sodium and meglumine diatrizoate or Hypaque-M, 75%) was injected into the coronary artery through the distal circumflex catheter or the Sones coronary arteriography catheter. The dose was sufficient for fluoroscopic opacification equivalent to that for clinical coronary angiography and was constant for each dog, averaging 3.1 cc (0.12 cc/kg). As demonstrated previously, intracoronary Hypaque-M, 75% in these doses causes a brief maximal increase in coronary flow equivalent to that following ten second occlusion. Before each injection, coronary flow, aortic and circumflex pressures were allowed to stabilize. Contrast was then injected while these variables were recorded continuously until all parameters returned to pre-injection levels. After stabilization again, the constrictor was tightened and contrast injection was repeated. In 14 to 22 such steps the constrictor was tightened to complete occlusion. In this manner the pressure-flow relationships of coronary constrictions were determined over a complete range of stenoses and flows. After completion of these steps, the constrictor was removed and flow allowed to stabilize. The test flow to ten second occlusion was measured again for comparison to the preexperiment response in order to demonstrate stability and responsiveness of the experimental animal. After removal of the flow transducer, 10 second occlusion was again performed to verify that the flow transducer produced no pressure gradient at peak hyperemia.

Mean values of pressures and flows were analyzed. Coronary stenoses were hemodynamically characterized by the slope of the regression line relating mean pressure gradient across the stenosis to mean coronary flow through it in cc/min during hyperemia. As subsequently shown, this method of characterizing or quantifying the hemodynamic effects of stenoses provided a single number which described an anatomically fixed lesion in terms of its pressure-flow consequences regardless of its physical dimensions, coronary flow, pressure gradient, or distal coronary bed resistance. Stenosis resistance was also calculated as previously described as pressure gradient across the stenosis divided by the flow through it in cc/min. Coronary vascular bed resistance distal to a stenosis was calculated as mean coronary perfusion pressure distal to the stenosis divided by mean coronary flow in cc/min.

Total micrometer excursion of the constrictor was determined as the difference between the baseline micrometer reading at zero lesion and the reading at 100% occlusion. Percent diameter constriction was then calculated for each intervening micrometer setting by the following equation:

\[ \text{% diameter stenosis} = \left( \frac{\text{micrometer reading at no lesion}}{\text{total micrometer excursion}} \right) \times 100 \]

Although the micrometer excursion measured circumference change, percent circumference change equals percent diameter change. All values for percent stenosis in this report refer to percent decrease in diameter.

Data were analyzed with a digital PDP-8 computer and regression lines plotted by least squares fitting to appropriate mathematical equations in order to draw smooth, mathematically accurate curves through plotted data points.

**Results**

The relationships between pressure gradient and flow during hyperemia were determined for 157 different stenoses. For each stenosis, coronary flow was varied from basal rates up to maximum (hyperemia) by intracoronary injection of Hypaque-M, 75%, as previously described. Examples of flow responses and pressure gradients during hyperemia following contrast injection in the presence of stenoses have been previously reported. Table 1 provides examples of flows and pressure gradients for randomly selected stenoses over 80% in this study. The pressure gradient across a stenosis was linearly related to flow through it over a range of flows from normal resting to maximum; r values were above 0.98. Representative examples are shown in figure 1. With progressive stenosis the slope or steepness of the pressure-flow relationship increased.

A method of hemodynamically characterizing coronary stenoses is important to the systematic or statistical evaluation of the adequacy of compensatory coronary vasodilatation in coronary arteries of different sizes and having different resting flow rates. Pressure gradients across stenoses are variable, depending on flow, as shown in figure 1, and cannot be used to quantify the effects of stenoses. Determination of stenosis resistance was therefore evaluated as a means of characterizing stenoses hemodynamically. For each of the experimental points shown in figure 1 for one animal, stenosis resistance was calculated as pressure gradient divided by flow. Each of the resulting resistance values are plotted as a function of

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flow in figure 2. The curves demonstrate that for an anatomically fixed stenosis, stenosis resistance varied over a wide range depending on flow. For example, the resistance of the 22% stenosis was 0.8 mm Hg/cc per minute at resting flow but was 3.7 mm Hg/cc per minute during peak hyperemia. Thus, there was no single resistance value characterizing the anatomically fixed stenosis. Consequently, resistance values were of little usefulness experimentally. Computer derived curves best fitting the experimental data shown in figure 2 indicate that resistance was a hyperbolic function of flow.

Since calculations of stenosis resistance were of limited value, the pressure gradient-flow relationship during hyperemia was used to quantify the hemodynamic effects of stenoses for purposes of correlating them with compensatory changes of the distal coronary vascular bed. The linear relationship for each stenosis shown in figure 1 is characterized by a constant slope which increases with increasing stenosis. This slope is expressed as mm Hg change of pressure gradient for each cc per minute change in coronary flow. For example, the 84% stenosis characterized hemodynamically in this manner was 0.56 mm Hg change for each cc per minute change in

### Table 1

**Examples of Circumflex Flows and Stenosis Gradients during Hyperemia Induced by Contrast Media**

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Flow, cc/min Rest</th>
<th>Flow, cc/min Hyper</th>
<th>Gradient, mm Hg Rest</th>
<th>Gradient, mm Hg Hyper</th>
<th>Percent Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>853</td>
<td>62</td>
<td>257</td>
<td>0</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>804</td>
<td>56</td>
<td>182</td>
<td>0</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>843</td>
<td>52</td>
<td>181</td>
<td>0</td>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>802</td>
<td>54</td>
<td>169</td>
<td>0</td>
<td>9</td>
<td>93</td>
</tr>
<tr>
<td>803</td>
<td>57</td>
<td>195</td>
<td>0</td>
<td>10</td>
<td>88</td>
</tr>
<tr>
<td>842</td>
<td>39</td>
<td>187</td>
<td>0</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>844</td>
<td>30</td>
<td>170</td>
<td>0</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>860</td>
<td>44</td>
<td>229</td>
<td>0</td>
<td>5</td>
<td>92</td>
</tr>
<tr>
<td>854</td>
<td>44</td>
<td>136</td>
<td>0</td>
<td>13</td>
<td>88</td>
</tr>
</tbody>
</table>

Abbreviations: Gradient = aorta to distal coronary artery pressure gradient; Hyper = values during hyperemia following intracoronary injection of contrast media.

**Figure 1**

Characteristic regression lines relating pressure gradient across a coronary stenosis to flow through it. Stenoses of 22%, 84%, and 87% diameter narrowing are illustrated. Correlation coefficients ($r$) for these relationships are above 0.99.

**Figure 2**

Relationships of stenosis resistance ($R_s$), calculated as absolute resting pressure gradient/flow, to flow through the stenosis. The curves best fitting the experimental data points are hyperbolas. The ranges of values obtained for an anatomically fixed stenosis at resting (lowest value) and at maximal flow (highest value) are shown.
flow at resting as well as at maximum flow. Thus, the characterization of stenoses as \( \Delta \) pressure gradient per \( \Delta \) flow was empirically independent of flow over the range observed whereas stenosis resistance defined as absolute pressure gradient divided by absolute flow was dependent on flow.

The usefulness of characterizing stenoses by the slope of the pressure gradient-flow relationship during hyperemia is further demonstrated in the next two figures. In figure 3, percent diameter stenosis is plotted against the slope of the pressure gradient-flow relationship or \( \frac{\text{d(gradient)}}{\text{d(flow)}} \), and against stenosis resistance (absolute gradient/flow) at resting flow. The slope of the gradient-flow relationship during hyperemia increased at relatively modest anatomic stenoses, indicating altered gradient-flow relationships. In contrast, stenosis resistance defined as absolute resting gradient/flow remained normal since there was no resting gradient for those stenoses despite altered gradient-flow relationships during hyperemia. These results indicate that the slope of the gradient-flow relationship is more sensitive than resistance values in detecting and characterizing the effects of subcritical coronary stenoses.

Since small changes in arterial diameter have major hemodynamic consequences for stenoses above 60%, the increased sensitivity of this method for hemodynamically characterizing a stenosis becomes more apparent if plotted against pressure gradient across the stenoses. Figure 4 demonstrates this point. Stenoses which were progressively increased to 85% narrowing demonstrated resting pressure gradients and large increases in the slope of the gradient-flow relationships whereas stenosis resistance defined as absolute gradient/flow showed relatively little change.

Figure 4 also illustrates a disadvantage of characterizing stenoses as the slope of the gradient-flow relationship. With stenoses of greater than 85%, the slope of the gradient-flow relationship became so steep that it was experimentally difficult to measure accurately. In this instance the resistance calculated as absolute gradient/flow may be the more accurate because stenoses above 85% cause large resting pressure gradients and changes in resting coronary flow. The dependence of resistance values on flow may remain a limitation to its usefulness however.

Table 2 shows the coronary pressure flow responses during hyperemia in the presence of stenoses averaging 92 ± 3% diameter narrowing which reduced coronary flow to 74 ± 20% of normal control values. Following the stimulus of intracoronary Hypaque injection in the presence of a stenosis, coronary flow increased 18% over resting levels in association with a 25% decrease in coronary pressure distal to the stenosis and a 37% decrease in coronary vascular resistance \((P < 0.001)\). This response indicates that vasodilatation of the coronary bed occurred in addition to that already present in compensation for the stenosis. The simultaneous pressure flow changes are conveniently expressed together as a ratio of coronary pressure/flow, i.e., vascular resistance, for purposes of correlations with severity of stenosis. In table 2 the percent changes shown are the means of changes for individual experiments and therefore may not exactly equal the percent change of mean values shown.

Figure 5 shows the compensatory changes of the distal coronary vascular bed in response to progressive proximal stenosis of coronary arteries. With progressive coronary constriction, the slope of the gradient-flow relationship of the stenosis did not in-
crease significantly until approximately 60% diameter reduction. Thus, resting coronary flow is not altered by constrictions up to 60% since there is no hydraulic resistance to flow. For lesions between 60% and 85% narrowing, the slope increased significantly and a resting gradient appeared but resting coronary flow remained normal because of a compensatory decrease in coronary vascular bed resistance. For lesions greater than approximately 85%, there was no further compensatory decrease in vascular bed resistance and resting flow fell precipitously with further coronary constriction.

Since small changes of severe stenoses have major hemodynamic effects, the compensatory changes of the distal vascular bed become more apparent if plotted against resting pressure gradient, as shown in figure 6. In effect this figure greatly expands that part of the previous figure for stenoses above 85%. It shows that when resting coronary flow was reduced to 74 ± 20% of normal control values by stenoses, calculated coronary vascular resistance was 1.46 ± 0.25 mm Hg/cc per minute or 64 ± 16% of the normal control resting value of 2.37 ± 0.71 mm Hg/cc per minute. Injection of contrast media resulted in further vasodilatation (table 2) and an additional further decrease in vascular resistance down to 0.91 ± 0.23 mm Hg/cc per minute or 40 ± 11% of normal resting values. With further narrowing, compensation by the distal bed fails and its resistance may actually increase if coronary pressure approaches the critical closing pressure of the vasculature distal to the stenosis. Minimum vascular resistance during hyperemia in the absence of stenosis was 0.53 ± 0.11 mm Hg/cc per minute or 23 ± 4% of resting control values.

Discussion

This study addresses the related problems of how to characterize coronary stenoses hemodynamically in a standard manner for experimental purposes, and how adequate are compensatory changes of distal coronary vascular bed resistance during progressive proximal stenosis of a coronary artery.

Shipley and Gregg, Fiddian et al., Cannon et al., and Logan et al. have shown that stenosis resistance calculated as pressure gradient/flow depends on vascular resistance distal to the stenosis and therefore on flow through the stenosis. Our results confirm these observations and demonstrate further that stenosis resistance is flow dependent over a range of coronary flows from normal resting to maximal in the intact animal and the relationship follows an hyperbolic curve. It is therefore of limited usefulness for characterizing the hemodynamic effects of a stenosis. We avoided this limitation by inducing hyperemia and determining the pressure gradient-flow relationship of a stenosis at elevated flows found during vasodilatation. Between normal resting and physiologically maximal coronary flow, the gradient-flow relationships of coronary stenoses were linear. The slope of the relationship was a fixed constant characterizing any anatomically fixed constriction independent of flow or distal resistance. Consequently, the numerical values of the gradient-flow slopes for different stenoses could be compared or statistically compiled.

At flows greater than the physiologic range and below normal resting values, as produced with a perfusion pump by Byar et al., the gradient-flow relationship is not linear. For example, the variable constrictor used in these studies was placed around a canine carotid artery having a distal shunt to the jugular vein. With a screw clamp on the shunt, fluid could be varied over a greater range than found in the intact coronary circulation. Within the range of flows corresponding to the range from normal resting to maximal physiologic coronary flow for a given stenosis, the gradient-flow relationship was essentially linear. However, particularly at lower flows the relationship became curvilinear toward zero. Empirically, the slope of the gradient-flow relationship during hyperemia was a useful means of hemodynamically characterizing a stenosis despite its non-linearity at below normal flow rates. For stenoses of greater than 85–90% diameter narrowing, which

### Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Flow, cc/min</th>
<th>Cor. pressure mm Hg</th>
<th>Gradient mm Hg</th>
<th>Cor. pressure/flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest, no stenosis</td>
<td>49 ± 8</td>
<td>110 ± 12</td>
<td>0</td>
<td>2.37 ± 0.71</td>
</tr>
<tr>
<td>Rest, stenosis</td>
<td>37 ± 14</td>
<td>53 ± 20</td>
<td>57 ± 17</td>
<td>1.46 ± 0.25</td>
</tr>
<tr>
<td>Hyperemia, stenosis</td>
<td>46 ± 22</td>
<td>38 ± 11</td>
<td>69 ± 7</td>
<td>0.91 ± 0.23</td>
</tr>
<tr>
<td>% Δ, hyperemia</td>
<td>+18 ± 20</td>
<td>−25 ± 12</td>
<td>+35 ± 53</td>
<td>−37 ± 16</td>
</tr>
</tbody>
</table>

Cor. = coronary; ± one standard deviation; % Δ is the mean of changes in individual experiments; + = increase; − = decrease.
Relationships of percent stenosis to resting coronary flow, distal vascular bed resistance, and the slope of the gradient-flow relationship during hyperemia. Coronary flow is expressed as percent of normal, control, resting coronary flow. Distal coronary vascular bed resistance is expressed as percent of resting, distal vascular bed resistance in the absence of stenoses. In compensation for progressive coronary constriction, distal vascular bed resistance reached a minimum of 64 ± 16% of control values. Reduced resting coronary flow, this approach was of limited usefulness.

Several reports have described autoregulation of coronary flow during coronary constriction or reduced coronary perfusion pressure in intact animals. Mosher et al.9 concluded that at low perfusion pressure the coronary bed was fully dilated. However, the minimum resistances of the distal vascular bed during normal hyperemia were not determined for comparison to those during reduced coronary perfusion pressure. Kjekhaus14 studied the effects of total occlusion rather than partial occlusion on autoregulative mechanisms; the relationship of compensatory changes to stenosis resistance could not be determined since constriction was complete. Khouri et al.3 concluded that with progressive stenosis resting coronary flow remained approximately normal until reactive hyperemia disappeared; his results imply that the distal vascular bed was maximally vasodilated in response to severe partial constriction. However, distal coronary pressure and vascular bed resistance distal to the constriction...
were not determined. Since the slope of the gradient-flow relationship is very steep for severe constrictions, small changes in flow are associated with major changes in pressure gradient and therefore distal perfusion pressure. In this circumstance vasodilatation with large changes in distal perfusion pressure and vascular bed resistance may therefore occur with little change in flow. Thus, flow measurements per se or the flow response during hyperemia may not accurately reflect altered vascular bed resistance or completeness of compensatory vasodilatation in the presence of severe stenoses.

Malindzak et al. have described resistance changes in response to partial coronary occlusion and tested the completeness of compensatory vasodilatation by giving vasodilators. They showed that at maximum coronary vasodilatation in response to partial stenosis, the coronary vascular bed dilated still further following nitroglycerin but there was no further increase in flow due to a fall in arterial pressure caused by nitroglycerin. However, since pressure gradients across the stenoses were not measured, resistance of the stenosis could not be determined separately from compensatory changes of the coronary vascular bed. Our results confirm and extend those of Malindzak et al.

Interpretation of Results

Hydraulic factors significantly influence the compensatory autoregulation of coronary artery inflow largely because of their effect on endocardial-epicardial flow distribution. Coronary flow redistributes from endocardium to epicardium with complete occlusion or partial stenosis of a coronary artery because of the fall in distal coronary pressure. In the presence of partial stenosis which reduces resting coronary flow, further vasodilatation or hyperemia results in an increase in coronary flow but a fall in coronary pressure (because of gradient-flow relationships across the stenosis) with a consequent worsening of endo-epicardial malperfusion. The over-all result of the increase in flow and decrease in coronary pressure may either improve or further compromise myocardial perfusion and function depending on the severity of stenosis and whether the stimulus for vasodilatation increases oxygen demands (pacing, exercise), decreases them (nitroglycerin, contrast media), or reduces endocardial extravascular compression.

The results of this study indicate that there was a vasodilator reserve present when total coronary artery blood flow was reduced by proximal stenoses. Since proximal stenosis reduces coronary pressure causing endocardial underperfusion the endocardium becomes relatively anoxic, with regional endocardial lactate production and fall in high energy phosphate content. In our experiments, therefore, the endocardium was probably maximally vasodilated, i.e., had no vasodilatory reserve. The epicardium maintained normal perfusion and the vasodilator reserve which we observed when total coronary artery flow was reduced by stenosis probably existed in the epicardium. The observation that injection of contrast material produced a further decrease in calculated coronary vascular resistance at the point that resistance values were minimal as coronary flow was reduced does not mean that further vasodilatation did not occur as flow was further reduced by increasing the stenosis. Our results suggest that during progressive coronary stenosis there was a continuous, progressive compensatory vasodilatation initially which was greatest in the endocardium, with some vasodilator reserve remaining in the epicardium. As the stenosis reached complete occlusion, the epicardium became maximally vasodilated also, as indicated by maximal coronary flow rates observed during the hyperemia following ten seconds of total occlusion.

Collateral blood flow into the areas distal to the occlusion tends to increase epicardial flow toward normal and to restore vasodilator reserve in the epicardium more than in the endocardium, as evidenced by worsening of endo-epicardial malperfusion of myocardium supplied collateralily after administration of vasodilators.

It is also important to consider the effects of extravascular pressure and the osmotic load of contrast media on the coronary vascular bed. The osmotic load causes a massive transfer of extravascular fluid into the intravascular space of the coronary bed which in turn causes a transient fall in coronary inflow during injection and appropriate changes in coronary sinus hematocrit, hemoglobin, protein concentration, and osmolality, with a decrease in myocardial oxygen consumption. The contrast media and fluids transferred into the intravascular space from the extravascular space drain into the coronary sinus leaving an "empty" vascular bed and reduced extravascular pressure. Consequently, a sudden marked increase in flow follows the transient decrease seen during injection, as long as coronary inflow remains unrestricted. However, if coronary inflow were restricted by a partial stenosis, coronary pressure falls markedly and the stenosis gradient increases in association with a smaller increase in flow than would occur in the absence of stenosis. Because of the steep pressure gradient-flow relationship characterizing severe stenoses, the increase in pressure gradient and fall in coronary pressure is proportionally greater than the increase in flow. In addition, marked regional malperfusion is seen following contrast injection in the presence of a stenosis but myocardial injury or
ischemia does not usually develop, probably because of the transience of these responses and because of the decreased myocardial oxygen requirements also caused by the presence of the contrast media. Malindzak observed similar pressure flow changes following administration of pharmacologic vasodilators. We have also found that intracoronary injection of adenosine triphosphate (ATP) produces the same pressure flow effects as contrast media in the presence of a stenosis severe enough to reduce resting coronary flow. Ball et al. have demonstrated that exercise in the presence of restricted coronary inflow redistributes coronary flow to the epicardium, results which indicate that epicardial vasodilator reserve may also be elicited by physiologic stimuli. We conclude that compensatory changes of the distal coronary vasculature in response to partial constriction are complexly related to hydrodynamic factors as well as hypoxic vasodilation and that vasodilator reserve present in the epicardium during partial constriction severe enough to reduce resting total coronary artery flow can be elicited by a variety of vasodilatory stimuli including exercise.

Critique of Methodology

There are several objections to using calculated coronary vascular resistance as a measure of compensatory vasodilatation distal to a constriction. As the constriction approaches complete occlusion, coronary flow approaches zero but coronary pressure does not fall below 10–20 mm Hg. Calculated vascular resistance then becomes “infinitely” large and is meaningless as a measure of distal bed vasodilatation. Furthermore, with release of a temporary complete occlusion coronary flow immediately increases to a maximum value (reactive hyperemia) thereby indicating maximal vasodilatation regardless of an “infinitely” large calculated vascular resistance during occlusion. For this reason it is necessary to evaluate the pressure-flow values per se before making conclusions based on resistance calculations. As shown in table 2, coronary flow increased and pressure distal to the stenosis fell following injection of Hypaque, thereby indicating further vasodilatation. This response can be conveniently described by the ratio of pressure/flow, i.e., calculated vascular resistance for purposes of comparison to severity of stenoses. The above objection does not apply to our data since values of calculated vascular resistance were associated with coronary flows that were nowhere near zero, i.e., 74 ± 20% of normal resting values. At some more severe, near complete stenosis, calculated vascular resistance becomes invalid as a measure of vasodilatation since flow approaches zero. This study was not designed to determine the point at which resistance calculations become invalid. Clearly, with the degree of stenoses in these experiments resistance values are valid since the basic pressure flow measurements indicate vasodilatation following Hypaque injection.

Values of calculated vascular resistance are dependent on coronary pressure distal to the stenosis. It is theoretically possible that failure to reach minimum values of calculated vascular resistance in response to coronary constriction may be due to collateral flow present or developing during the 1–2 hours of partial stenosis in each experiment; collateral flow would maintain high coronary pressure distal to the stenosis and thereby high values of calculated vascular resistance. This theoretical objection to values of calculated vascular resistance may be ruled out by the changes in distal coronary pressure per se rather than resistance values. Coronary pressure distal to the partial stenosis which reduced coronary flow to 74 ± 20% of normal was 53 ± 20 mm Hg (gradient 57 ± 17 mm Hg). Following intracoronary Hypaque injection, distal coronary pressure fell to 38 ± 11 mm Hg (gradient 69 ± 7 mm Hg) indicating additional vasodilatation beyond that occurring in compensation for partial stenosis severe enough to reduce resting flow. Furthermore, if collateral flow was sufficiently developed to maintain distal pressure at 55 mm Hg and thereby prevent any further pressure fall or any further decrease in minimum calculated vascular resistance, then distal coronary pressure should have been maintained at 55 mm Hg by that collateral flow during complete occlusion. However, in our study distal coronary pressure fell to 17 ± 8 mm Hg distal to complete occlusion, indicating little significant collateral flow. By contrast, coronary pressures of 50 to 70 mm Hg distal to complete occlusion are characteristic of developed collateral flow. In normal dogs during acute coronary occlusion, collateral flows and collateral conductance are probably very low or unmeasurable in the first 6–7 hours after occlusion and do not result in significant amounts of blood to the region of occlusion, in contrast to gradual occlusions in which collaterals have time to develop. The issue of collateral flow after acute occlusion is not entirely settled, however. Some reports have demonstrated significant collateral flow after acute occlusion. Regardless of the presence of collateral supply, our data document the presence of vasodilator reserve during lowered coronary flow.

There is one final question related to the methodology of this study. Why did contrast injection which decreased calculated vascular resistance to 23% of normal during no stenosis decrease calculated vascular resistance to 40% during partial stenosis which reduced coronary flow to 74% of normal levels?
Since we have not systematically studied the osmotic effects of contrast media on the myocardial bed with and without stenosis, we have no satisfactory answer. The vasodilatory effects of contrast are due to its osmotic properties and are therefore related to concentration of contrast media as well as its duration in the coronary bed, i.e., a complex dose-time relationship exists. A severe stenosis of the circumflex coronary artery will reduce resting flow distribution to that artery compared to the anterior descending. Contrast media injected into the main coronary will then be preferentially distributed to the anterior descending with a lesser dose of contrast media reaching the circumflex bed. Thus, the hyperemic response to contrast media will be reduced in the circumflex not only because the stenosis limits maximum coronary flow but also because the dose or stimulus for hyperemia is somewhat less than the dose reaching the nonstenotic artery. In addition, a given amount of Hypaque will have greater vasodilatory effects if delivered rapidly than if delivered slowly to the coronary bed. For example, 2 cc of Hypaque given over 8–10 seconds may produce less than half of the hyperemia produced by 2 cc given over 2 seconds. Similarly, with reduced coronary flow due to stenosis, the rate at which Hypaque is washed into the coronary bed is reduced and the hyperemic response may be correspondingly less. Although a given contrast injection may cause a somewhat less than a maximal response during reduced coronary flow for whatever complex reasons, the stimulus is still sufficient to increase coronary flow and thereby demonstrate vasodilatory reserve available beyond that used in compensation for partial stenosis.

Clinical Implications

The hydraulic effects of a stenosis reportedly depend in a complex fashion on absolute diameter of the lumen of a stenosis. Poiseuille’s equation has been used to describe this relationship mathematically; it relates the resistance or pressure gradient of a stenosis to the inverse of the fourth power of the absolute radius. However, it has been demonstrated that Poiseuille’s equation is not applicable to segmental arterial stenoses and a recent report suggests that relative rather than absolute stenosis is critical. This problem is of practical importance to the angiographer. For example, by the hydraulic equations previously used, the resistance and pressure gradient caused by 70% constriction of a 3 mm diameter artery is greater than that caused by 70% constriction of a 5 mm diameter artery having the same flow velocity. How significant or whether greater depends on the equations applied. The problem is also pertinent to the anatomic criteria of 70–80% stenosis often used for deciding to implant coronary bypass grafts. If the hydraulic effects of stenoses were dependent on absolute and not relative lumen diameter, these criteria might not apply equally well to arteries of different sizes. Unfortunately, absolute stenosis radius cannot be reliably measured from arteriograms because of varying magnification in different views and at different parts of the artery at different distances from the X-ray tube. Additional problems arise in the presence of an eccentric lesion which may appear as a 40% narrowing in one view and as an 80% narrowing in another view.

Despite relatively severe stenoses, resting coronary flow remains normal as a consequence of both hydraulic characteristics of stenoses and of compensatory changes of the distal coronary vascular bed which develop for stenoses above 60% but are relatively ineffective for stenoses above 85%. However, vasodilatory reserve is still present in the presence of stenoses which reduce resting coronary flow. Induced vasodilatation in the presence of severe stenosis has deleterious effects on endocardial-epicardial flow distribution which may lead to a vicious cycle of further ischemia and vasodilatation in layers of myocardium nearer the epicardium which cause further coronary pressure fall leading in turn to more ischemia and vasodilatation. Such a vicious cycle would explain why patients with chronic, anatomically stable coronary disease might develop a myocardial occlusion or thrombosis, particularly a subendocardial infarction. It would also provide a mechanism for the prolonged resting pain of unstable angina which is not relieved by nitroglycerin. Whether further vasodilatation benefits the myocardium in the presence of a partial stenosis depends on the severity of stenosis, distal coronary pressure, pressure gradient-flow relationships, extravascular compression, and the type and degree of stimulus for vasodilatation.

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