LABORATORY INVESTIGATION
MYOCARDIAL OXYGEN SUPPLY

Effect of a reduction in blood viscosity on maximal myocardial oxygen delivery distal to a moderate coronary stenosis

ALBERT S. MOST, M.D., NICHOLAS A. RUOCO, JR., M.D., AND HENRY GEWIRTI, M.D.

ABSTRACT This study tested the hypothesis that a reduction in blood viscosity by means of isovolumetric hemodilution will permit an increase in maximal oxygen delivery to myocardium distal to a moderate coronary arterial stenosis. It is known that blood viscosity is a determinant of resistance to blood flow at both the stenotic and the arteriolar levels. Accordingly, a reduction in blood viscosity could exert a favorable influence on maximal myocardial oxygen delivery in the setting of stenosis, provided that the oxygen-carrying capacity of the blood is not compromised excessively. Closed-chest, sedated domestic swine (n = 8) were instrumented with an artificial coronary arterial stenosis that reduced vessel diameter by 64%. Measurements of hemodynamics, regional myocardial blood flow (microspheres), lactate and oxygen metabolism, and whole blood viscosity were made at control and after two successive 10 min intracoronary infusions of adenosine (400 and 800 µg/min) distal to the stenosis. Next, albumin/saline solution was given intravenously to reduce the animal's hematocrit by approximately 50%. Repeat measurements of all experimental variables were then made at a second control and again after two successive 10 min intracoronary infusions of adenosine (400 and 800 µg/min) distal to the stenosis. Myocardial blood flow (ml/min/g) distal to the stenosis increased from 1.52 ± 0.21 (mean ± 1 SD) to 4.10 ± 0.86 in response to adenosine (peak dose) before hemodilution (p < .01) and from 2.07 ± 0.59 to 4.08 ± 0.93 (p < .01) after hemodilution. Minimum resistance (mm Hg/ml/min/g) distal to the stenosis, however, was approximately 33% lower (p < .05) during infusion of adenosine after hemodilution than it was before hemodilution (endocardium 15.8 ± 6.3 vs 24.5 ± 14.1 and epicardium 9.0 ± 2.3 vs 14.0 ± 8.0). Maximal oxygen delivery (ml/min/100g) to myocardium distal to the stenosis failed to improve and in fact was reduced (p < .01 vs before hemodilution) after hemodilution (34.6 ± 9.5 vs 19.9 ± 6.8 to endocardium and 65.5 ± 16.4 vs 38.0 ± 10.5 to epicardium). Regional myocardial lactate metabolism, however, did not change vs initial control during the study. Finally, hematocrit was reduced from 32 ± 3% to 17 ± 3% (p < .01) and blood viscosity was reduced from 3.4 ± 0.2 to 2.4 ± 0.3 centipoise (p < .01) by hemodilution. The results of the study indicate that reducing blood viscosity by isovolumetric hemodilution may not enhance maximal myocardial oxygen delivery in the setting of a moderate coronary arterial stenosis. However, because minimal endocardial resistance is lowered by a reduction in blood viscosity, it is likely that maximal oxygen delivery could be improved by this intervention if hemodilution were accomplished with a fluid capable of transporting oxygen (e.g., perfluorocarbon emulsion).


DELIVERY OF OXYGENATED blood to the myocardium in the setting of a coronary arterial stenosis is influenced by a number of factors. Many of these (e.g., stenosis dimensions, heart rate, and perfusion pressure) have been investigated in considerable detail in earlier studies. Rheologic factors, however, have received relatively little attention. It is known that for any given level of flow across a coronary stenosis the pressure gradient required to maintain flow increases as the viscosity of blood increases,1,2 and that effective resistance to flow also increases at the arteriolar level as blood viscosity increases.3,4 At shear rates equal to or greater than 100/sec (representative of values observed in the coronary circulation5,6), blood viscosity is independent of shear rate and is primarily a function of hematocrit and fibrinogen concentration.3,4,7 These

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considerations suggest the hypothesis that maximal oxygen delivery to myocardium distal to a coronary stenosis may be improved by reducing blood viscosity, particularly if the oxygen-carrying capacity of the blood is not compromised excessively. We tested this hypothesis in a series of closed-chest, sedated, domestic swine instrumented with an artificial coronary arte-
rial stenosis that reduced luminal diameter of the vessel by 64%. Isovolumetric hemodilution with albumin/saline solution was used to reduce blood viscosity. A moderate reduction in coronary diameter was chosen to create conditions in which a definite increase in myocardial blood flow distal to the stenosis could occur. Each animal was studied both at rest and under conditions of maximal coronary vasodilation (intracor-
ary adenosine) before and after hemodilution.

Materials and methods

Animal preparation. Farm-bred pigs (n = 8, mean weight = 42 kg, range = 37 to 51 kg) were anesthetized with ketamine (25 mg/kg im), placed on a volume-cycled respirator, and venti-
lated with 0.5% to 1.5% halothane and nitrous oxide (60:40 mixture with oxygen). Respiratory tidal volume and frequency were adjusted to maintain arterial blood gases and pH within the physiologic range. Fluid-filled No. 7F catheters were posi-
tioned under fluoroscopic guidance in the descending aorta, left atrium, and anterior interventricular vein (AIV). The latter was carefully positioned in each case to lie adjacent or distal to the stenosis (see below) to ensure selective sampling of venous effluent from the zone of myocardium distal to the stenosis. A rigid coronary arterial stenosis was placed in the left anterior descending coronary artery (LAD) by use of a technique de-
scribed in detail elsewhere. The stenosis reduced the diame-
ter of the coronary lumen by 64%. A small fluid-filled catheter was placed in the stenosis and throughout this catheter pressure distal to the stenosis was recorded and adenosine was infused according to the experiment protocol. The results of a “pop” test performed on the infusion catheter (reported previously) demonstrated that 90% or more of the phasic information present in the distal coronary pressure waveform could be registered by the catheter. A single electrocardiographic lead was affixed to mon-
tor heart rate. A pacing catheter was placed in the right atrium to maintain a constant heart rate during each study. Finally, a micromanometer-tipped catheter was placed in the left ventricle and was balanced and calibrated with respect to the fluid-filled catheter in the aorta.

After all catheters and the stenosis were placed, the animals were allowed to partially awaken from anesthesia until they were breathing spontaneously and had brisk corneal reflexes. Subsequently, small doses of sodium thiamylal were adminis-
tered intravenously to keep the animals quiet and free of pain. Animals were fully anticoagulated with heparin and received aspirin (325 mg iv) to sustain patency of the coronary stenosis.

Study protocol. The protocol consisted of two identical sets of interventions, one under control conditions and the other during hemodilution. In the control condition, aortic, left ventricular, and left atrial pressures were recorded in addition to coronary arterial pressure distal to the stenosis. Arterial and AIV blood samples were drawn for lactate and oxygen determinations and blood flow was measured with radiolabeled microspheres (for methods see below). An intracoronary infusion of

adenosine (distal to the stenosis) was initiated for 10 min at 400 μg/min (0.34 ml/min), after which similar pressure measurements, flow determination, and blood sampling were repeated. A 10 min, an 800 μg/min infusion followed (0.34 ml/min), and repeat measurements and blood samples were obtained at its conclusion. After this protocol, a phlebotomy was carried out in each animal with equivalent replacement of blood with a saline-albumin solution. The solution consisted of 3 g bovine serum albumin dissolved in 100 ml normal saline adjusted to pH 7.45 with sodium bicarbonate. Hematocrit was lowered by 40% to 50%. Once hemodilution of this degree was achieved, the same baseline and two adenosine infusion protocols were carried out. At the conclusion of the study protocol, marker microspheres were injected through the catheter to mark the region perfused by the stenosed portion of LAD. This region of left ventricular myocardium, the LAD zone, was therefore identified for subsequent comparison with a remote, unlabeled region perfused by the left circumflex coronary artery (LCX). Once the marker microsphere infusion was completed each animal was given a large intravenous dose of sodium thiamyl and 5 min later was killed with an intravenous injection of KCl.

Hemodynamic measurements. All data were obtained with a Hewlett-Packard eight-channel recorder (Model 7788A). In addition, output from pressure transducers and the electrocardiographic amplifier were digitized on-line and subsequently analyzed as previously described. A PDP 11/40 computer system was used for data acquisition and analysis. All hemodynamic measurements were made based on an average cardiac cycle (10 sec data acquisition) constructed by the computer. Tension-time index (mm Hg/sec) was taken as the area under the systolic portion of the left ventricular pressure trace.

Regional myocardial blood flow. For each experimental condition approximately 4 × 10⁶ radiolabeled microspheres (15 μm diameter, 85 to 105 μCi total radioactivity) were injected via the left atrial catheter to determine regional myocardial blood flow. A different radioisotope was chosen at random for each flow determination. Microspheres were suspended in 2 ml of 20% dextran with 0.01% Tween-80 and mechanically dis-
persed by repeated injection between stock vial and syringe for 2 min before each injection.

The anterior free wall along with the posterior and lateral walls of the left ventricle were removed from the excited 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 was carefully noted on a diagram of the free wall of the ventricle. Each cube was divided into endocardial and epicardial halves. Each endocardial and epicardial half was again divided in half to obtain endocardial and epicardial layers that represented the innermost and outer-
most quarters of the left ventricular wall, respectively. Each quarter of the transmural cube weighed between 0.25 and 0.75 g. Radioactivity was measured in a gamma well counter (Pack-
ard Instruments, Downer Grove, IL). A computer was used to correct for spillover of counts from one isotope into the window of another and to calculate regional myocardial blood flow in each tissue sample.

Tissue samples from the free wall of the left ventricle in the distribution of the LAD that received the drug infusion were designated as being from the distal zone. These samples were readily identified because each contained a high concentration (≥7000/g) of marker microspheres. Tissue samples (n = 10 to 20 transmural cubes) obtained from myocardium at the postero-
basal region of the left ventricle perfused by the nonstenosed LCX also were analyzed. This region of the left ventricle (designated the circumflex zone) was used as a reference area because it was physically remote from the distal zone and contained no marker microsphere radioactivity.
Flow values 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 values, 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 values for each of the four quarters comprising the cube. Tissue samples that exhibited control flow values greater than 2 SDs below mean flow for the distal zone were considered to be severely ischemic and were thus excluded from analysis.

Coronary arteriolar resistance in endocardium distal to the stenosis was calculated by dividing distal coronary mean diastolic pressure minus mean left atrial pressure plus 7 mm Hg by distal zone endocardial blood flow. Distal zone epicardial and transmural resistances were calculated in the same fashion except for the fact that distal coronary mean pressure and distal zone epicardial and transmural flows, respectively, were used in the computation. Resistances in the circumflex zone were calculated with the use of aortic instead of distal coronary pressure. Effective backpressure in the coronary circulation was taken as mean left atrial pressure plus 7 mm Hg based on experimental data of Pantley et al.11

Resistance at the level of stenosis was calculated as follows:

\[
\text{Stenosis resistance} = \frac{\text{mean aortic pressure} - \text{mean distal coronary pressure}}{\text{LAD transmural flow}}
\]

**Regional myocardial oxygen metabolism.** Paired samples (2 to 3 ml) of arterial and anterior interventricular venous blood were obtained for determination of oxygen content (Lex-O2CON Instrument, Lexington Instruments, Waltham, MA) during each phase of the study. Oxygen content (vol %) was determined in duplicate for each sample and values were accepted only if the difference between them was 0.2 ml O2/dl or less. Regional myocardial oxygen consumption was calculated as the product of transmural regional myocardial blood flow distal to the stenosis and the arterial-AIV lactate difference.

**Blood viscosity.** Hematocrit of venous blood was determined by the standard capillary tube/microcentrifuge technique at each stage of the study protocol. Viscosity of whole blood was measured with a Wells-Brookfield microviscometer over a range of shear rates (10 to 200/sec). Each determination was performed at constant temperature (37°C) and in duplicate or triplicate if duplicate values differed by more than 10%. The viscometer was calibrated with oils of known viscosity. Values of blood viscosity measured at shear rate of 90/sec were used in the data analysis because (1) average shear rate in the coronary circulation is roughly of this order;5,6 and (2) viscosity of blood is essentially independent of shear rate above this level.5,7 Viscosity measurements were carried out at each stage of the protocol.

**Statistical analysis.** All data are expressed as the mean ± SD. To facilitate analysis only data obtained at the dose of adenosine that produced the maximal reduction in endocardial resistance distal to the stenosis were analyzed. Before hemodilution, this was the 800 μg/min dose for six of eight animals and after hemodilution this dose produced maximal reduction in five of the eight animals. In five animals the dose level was the same under each condition (800 μg/min in four of five). The significance of differences in group mean values was assessed by means of blocked one-way analysis of variance and the Newman-Keuls multiple comparison test.12 It should be noted, however, that stenosis resistance as well as minimal resistances distal to the stenosis before and after hemodilution were directly compared with one another after log transformation (to minimize variances) and without consideration of respective control values. This is equivalent to performing a paired t test. The same procedure (except for log transformation) also was used for maximal oxygen delivery distal to the stenosis before and after hemodilution. Values of p < .05 were considered statistically significant.

**Results**

**Rheology.** As intended, hematocrit of venous blood was reduced from 32 ± 3% to 17 ± 3% (p < .01) by hemodilution. Blood viscosity (centipoise) at a shear rate of 90/sec declined from 3.4 ± 0.2 to 2.4 ± 0.3 (p < .01) after hemodilution.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Hemodynamic data (mean ± 1 SD)</td>
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<table>
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<tr>
<th></th>
<th>Before hemodilution</th>
<th>Hemodilution</th>
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<tbody>
<tr>
<td></td>
<td>Control 1</td>
<td>Adenosine 1</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>115 ± 9</td>
<td>115 ± 8</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>114 ± 10</td>
<td>111 ± 10</td>
</tr>
<tr>
<td>Distal coronary pressure (mm Hg)</td>
<td>Overall mean</td>
<td>106 ± 13</td>
</tr>
<tr>
<td></td>
<td>Diastolic mean</td>
<td>103 ± 13</td>
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<tr>
<td></td>
<td>Stenosis gradient (mm Hg)</td>
<td>9 ± 5</td>
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<tr>
<td></td>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>12 ± 5</td>
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<td></td>
<td>Tension-time index (mm Hg)</td>
<td>35.4 ± 3.1</td>
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</table>

LV = left ventricular.

ᵇp < .05 vs control 1; ᵇp < .01 vs control 1; ᵇp < .01 vs control 2.
Hemodynamics (table 1). Heart rate was held constant by atrial pacing throughout the study. The infusion of adenosine caused a significant (p < .05) reduction vs control in left ventricular end-diastolic pressure before hemodilution. However, both aortic mean pressure and tension-time index remained unchanged during the initial infusion of adenosine. As anticipated the transstenotic gradient increased significantly vs that at control in response to adenosine before hemodilution.

After hemodilution had been accomplished, there was a significant (p < .05) reduction vs prehemodilution levels in aortic mean pressure, tension-time index, and left ventricular end-diastolic pressure. None of these variables, however, changed significantly vs those at control 2 in response to the second infusion of adenosine. Finally, the transstenotic pressure gradient increased significantly (p < .01) vs that at control 2 in response to adenosine and did not differ significantly from that observed during the infusion of adenosine before hemodilution.

Regional myocardial blood flow (table 2). Before hemodilution, flow in all myocardial layers distal to the stenosis increased in response to adenosine. Epicardial flow, however, increased more than endocardial flow, and as a result, the endocardial/epicardial flow ratio declined significantly (p < .01) vs control. Flows in the circumflex region did not change vs those at control during the infusion of adenosine.

At control 2 after hemodilution there was a significant (p < .05) increase vs the value at control 1 in circumflex zone flow in all myocardial layers. Although flows in all layers of the myocardium distal to the stenosis also tended to increase vs those at control 1 after hemodilution (i.e., at control 2), only the increase in distal zone endocardial flow was statistically significant (p < .05). Infusion of adenosine distal to the stenosis after hemodilution resulted in a substantial increase in epicardial and transmural flow (p < .01), but only a modest and statistically insignificant rise in endocardial flow. Flow in all layers of the myocardium distal to the stenosis during the trial of adenosine with hemodilution was comparable to (but not greater than) that observed during adenosine before hemodilution.

Stenosis and coronary vascular resistance (table 3). Before hemodilution both endocardial and epicardial resistance distal to the stenosis declined significantly (p < .01) in response to adenosine. After hemodilution both endocardial and epicardial resistance distal to the stenosis declined (p < .01) vs control 1 levels. After hemodilution the infusion of adenosine also resulted in a significant (p < .01) reduction vs control 2 in both endocardial and epicardial resistance. In addition, values of endocardial and epicardial resistance observed during infusion of adenosine after hemodilution were significantly (p < .05) less than those observed during adenosine alone.

Stenosis resistance increased vs that at control 1 in response to adenosine. After hemodilution stenosis resistance did not differ significantly from that at control 1. Similarly, the administration of adenosine after hemodilution was accompanied by a significant increase in stenosis resistance. Stenosis resistances during adenosine and hemodilution did not differ from that observed during adenosine alone.

Myocardial oxygen delivery (table 4). Adenosine produced a substantial increase (p < .01) vs the control value in myocardial oxygen delivery in both endocardium and epicardium distal to the stenosis. Myocardial oxygen extraction during the infusion of adenosine declined (p < .01) vs that at control, while oxygen delivery increased (p < .01) but not significantly vs control 1 levels. There was a significant decrease vs the value at control 1 in myocardial oxygen delivery distal to the stenosis after hemodilution.
Data on coronary vascular resistance (mm Hg/ml/min/g; mean ± 1 SD)

<table>
<thead>
<tr>
<th>LAD zone</th>
<th>Control 1</th>
<th>Adenosine 1</th>
<th>Control 2</th>
<th>Adenosine 2</th>
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</thead>
<tbody>
<tr>
<td>Endocardium</td>
<td>61.6±7.8</td>
<td>24.5±14.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.9±11.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15.8±6.3&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Epicardium</td>
<td>70.5±14.8</td>
<td>14.0±8.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41.7±10.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.0±2.3&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Transmural</td>
<td>62.4±8.7</td>
<td>16.5±7.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38.4±9.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.6±2.2&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<tr>
<td>Circumflex zone</td>
<td></td>
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<tr>
<td>Endocardium</td>
<td>60.8±8.0</td>
<td>54.9±13.5</td>
<td>37.3±9.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35.2±5.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Epicardium</td>
<td>74.9±10.2</td>
<td>69.6±20.3</td>
<td>45.2±9.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44.0±6.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Transmural</td>
<td>66.1±7.6</td>
<td>60.6±16.1</td>
<td>40.6±8.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38.7±5.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stenosis</td>
<td>6.2±4.5</td>
<td>9.7±4.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.0±2.8</td>
<td>8.7±3.0&lt;sup&gt;b&lt;/sup&gt;</td>
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All LAD zone resistances (endocardial, epicardial, and transmural) at Adenosine 2 were less (p < .05) than respective values at Adenosine 1.

<sup>a</sup>p < .01 vs control 1; <sup>b</sup>p < .01 vs control 2.

Data on regional myocardial oxygen metabolism (mean ± 1 SD)

<table>
<thead>
<tr>
<th></th>
<th>Before hemodilution</th>
<th>Hemodilution</th>
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<tbody>
<tr>
<td></td>
<td>Control 1</td>
<td>Adenosine 1</td>
</tr>
<tr>
<td>Arterial O&lt;sub&gt;2&lt;/sub&gt; content (vol %)</td>
<td>13.7±1.2</td>
<td>13.1±1.3</td>
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<tr>
<td>AIV O&lt;sub&gt;2&lt;/sub&gt; content (vol %)</td>
<td>2.2±0.8</td>
<td>8.7±2.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Myocardial O&lt;sub&gt;2&lt;/sub&gt; extraction (%)</td>
<td>84±6</td>
<td>27±4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Myocardial O&lt;sub&gt;2&lt;/sub&gt; consumption (ml/min/100 g)</td>
<td>17.6±3.7</td>
<td>17.2±8.1</td>
</tr>
<tr>
<td>LAD zone O&lt;sub&gt;2&lt;/sub&gt; delivery (ml/min/100 g)</td>
<td>20.8±3.6</td>
<td>34.6±9.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Endocardium</td>
<td>19.0±4.8</td>
<td>65.5±16.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Epicardium</td>
<td></td>
<td>14.7±4.4</td>
</tr>
</tbody>
</table>

Values for oxygen delivery to endocardium and epicardium distal to the stenosis during Adenosine 2 were consistently less (p < .01) than corresponding values during Adenosine 1.

<sup>a</sup>p < .05 vs control 1; <sup>b</sup>p < .01 vs control 1; <sup>c</sup>p < .01 vs control 2.
not change significantly during administration of adenosine after hemodilution.

Discussion

We tested the hypothesis that reducing blood viscosity by isovolumetric hemodilution may improve maximal myocardial oxygen delivery distal to a moderate coronary arterial stenosis by reducing the effective resistance to blood flow both at the stenosis and the arteriolar level. The hypothesis in effect proposes that the loss in oxygen-carrying capacity of the blood caused by hemodilution will be more than offset by improved flow resulting from the reduction in blood viscosity. The results of the study, however, indicate that even in the face of a moderate stenosis flow may not increase sufficiently to offset the loss of oxygen-carrying capacity caused by hemodilution. This conclusion holds even allowing for the possibility that after hemodilution peak blood flow and maximal oxygen delivery to myocardium distal to the stenosis would likely have been roughly 20% greater than observed had aortic mean pressure not declined by 20% during hemodilution.

It is important to emphasize, however, that under basal conditions in the present study hemodilution sufficient to reduce hematocrit by roughly 50% did not cause any evidence of impairment of myocardial oxygenation. This reflects the fact that vasodilator reserve distal to the stenosis, particularly in the endocardium, was adequate to permit flow to increase sufficiently to satisfy prevailing levels of myocardial oxygen demand. Hemodilution and associated loss of oxygen-carrying capacity of the blood presumably provided the stimulus for coronary vasodilation under control 2 conditions before the administration of adenosine. However, the fact that endocardial and epicardial resistances distal to the stenosis were roughly 33% lower during adenosine after hemodilution than before (table 3) indicates that reduced blood viscosity per se can augment the flow reserve of the arteriolar bed and thereby contribute to maintenance of adequate myocardial oxygenation.

Since conclusions regarding the influence of hemodilution on coronary flow reserve are based primarily on calculated values of coronary vascular resistance, it is appropriate to consider potential limitations of such calculations. In the present study, all of the variables used in making the calculations were directly measured at each phase of the experiment, with one exception. Since it was impossible to measure zero flow pressure at every phase of the study, we used measured left ventricular end-diastolic pressure plus 7 mm Hg based on data obtained by Pantely et al.11 in fully vasodilated (intracoronary adenosine) domestic swine. While it is true that zero flow in the coronary circulation may be influenced importantly by changes in coronary tone,13, 14 data from two previous studies11, 15 indicate that, under conditions of maximal coronary vasodilation, zero flow pressure changes very little over the range of left ventricular diastolic pressures (average 4 to 12 mm Hg) encountered during administration of adenosine in the present study. Furthermore, previous studies also have shown that under conditions of maximal coronary vasodilation a decline in coronary perfusion pressure may be associated with a decline in coronary conductance or an increase in resistance15, 16 compared with levels observed at higher perfusion pressures. In light of the above considerations it is reasonable to conclude that (1) calculated resistance values likely provide appropriate estimates of resistance to flow in the coronary circulation in the present study, and (2) the estimate of the extent to which hemodilution improved the vasodilative reserve of the distal coronary bed may be conservative since coronary perfusion pressure during adenosine plus hemodilution was reduced vs that after adenosine infusion but before hemodilution.

Unfortunately, as long as hemodilution is accomplished with fluids devoid of oxygen-carrying capacity, enhanced flow reserve resulting from reduced blood viscosity may be offset by a reduction in oxygen transport. It is not immediately obvious, however, at what point an unfavorable balance will develop. In the present study it was demonstrated that, in the setting of
a moderate stenosis (85% to 90% cross-sectional area reduction), myocardial oxygen demand on the order of 20 to 40 ml/min/100 g can be met with an hematocrit as low as 17%. It is not likely that higher levels of myocardial oxygen demand would have been as well tolerated.17 Similarly, different (and possibly more favorable) results might have been obtained if the oxygen-carrying capacity of the blood had been reduced less or if hemodilution had been undertaken from a substantially higher baseline hematocrit (e.g., 60% to 70%).

Previous investigators have studied the effects of abrupt changes in hematocrit on coronary flow and resistance. In the nonstenosed canine coronary circulation it has been demonstrated that (1) minimal coronary vascular resistance increases as hematocrit is raised from 30% to 70%,18 and (2) changes in blood viscosity induced by alterations in hematocrit over a wide range (20% to 60%) can account almost entirely for observed changes in vascular resistance.19 The results obtained in the present study are consistent with and also extend these observations. In the nonstenosed coronary circulation the principal resistance to flow resides at the arteriolar level. Under these conditions lowering arteriolar resistance by hemodilution does not carry with it the risk of reducing coronary perfusion pressure, which could occur in the stenosed coronary circulation as a result of increased turbulence generated at the site of the stenosis. Since pressure loss across a coronary arterial stenosis changes linearly with viscosity but geometrically with turbulence,1 2 it is not easy to know a priori how hemodilution will affect myocardial blood flow and oxygen delivery in the setting of stenosis. Any gain made in terms of decreasing pressure loss across the stenosis as a result of reducing blood viscosity in theory could be offset by simultaneous enhancement of turbulence as blood exits the stenosis.* In the present study there was no difference in stenosis resistance during adenosine before and after hemodilution, despite the fact that blood viscosity was reduced by one-third (i.e., from roughly 3 to 2 centipoise at shear rate of 90/sec) and transstenotic flow was nearly identical with each trial. Thus, marked hemodilution, even when accompanied by a substantial increase in transstenotic blood flow, may not be accompanied by an increase in the transstenotic pressure gradient (compared with prehemodilution vasodilation) and hence an added reduction in perfusion pressure to the distal bed. This could reflect the fact that development of turbulent flow is influenced more by stenotic geometry than by fluid viscosity. In summary, the effects of a reduction in blood viscosity tend to cancel each other out at the level of stenosis rather than either increasing or decreasing the pressure gradient required for a given level of flow.

Clinical implications. Since hemodilution may reduce the thrombogenicity of blood,20 it is possible that, in the setting of a moderate coronary arterial stenosis, this intervention would be useful in preventing or delaying recurrent coronary thrombosis in patients who have been treated with thrombolytic agents for acute myocardial infarction. In addition, the principal limitation of hemodilution (i.e., loss of oxygen-carrying capacity) could be overcome by dilution with perfluorocarbon or other oxygen-transporting fluids instead of albumin/saline solution. Indeed, recent experiments in canine preparations of myocardial infarction demonstrate that size of infarction can be reduced by use of perfluorocarbon emulsions.21 22 Maintenance of the oxygen-carrying capacity of diluted blood by administration of artificial blood substitutes and supplemental oxygen would, in principle, expand the range of clinical conditions in which the intervention could be applied, since patients with more severe stenoses and/or higher myocardial oxygen demands than modeled in this study could be treated. Additional animal experiments will be required before such interventions can be applied to humans.

In conclusion, this study tested the hypothesis that reduction of blood viscosity by isovolumetric hemodilution will result in an overall improvement in maximal myocardial oxygen delivery distal to a moderate coronary arterial stenosis. We demonstrated under basal conditions that substantial hemodilution did not compromise myocardial oxygenation, even though the intervention failed to improve the maximal oxygen transport capability of the stenosed coronary circulation. Hemodilution did not alter stenotic resistance either at rest or after adenosine-induced coronary vasodilation. It did, however, lower minimal arteriolar resistance by approximately 33% after intracoronary administration of adenosine. Accordingly, the data suggest that maximal oxygen transport may be improved by hemodilution in the setting of stenosis, provided that systemic arterial pressure and oxygen-carrying capacity of the blood are maintained at near-control levels. Artificial blood substitutes such as perfluorocarbon emulsions could be used to accomplish these ends.24

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*The critical velocity (Vc) at which fluid flow in a cylindrical tube becomes turbulent is directly proportional to the viscosity of the fluid.20 Thus, \( Vc = \) Re/\( \rho \), where \( \rho \) = Reynolds number; \( N = \) viscosity; \( \rho = \) fluid density; \( D = \) tube diameter.
References
Effect of a reduction in blood viscosity on maximal myocardial oxygen delivery distal to a moderate coronary stenosis.
A S Most, N A Ruocco, Jr and H Gewirtz

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