Autologous blood perfusion for myocardial protection during coronary angioplasty: a feasibility study

KENNETH G. LEHMANN, M.D., J. EDWIN ATWOOD, M.D., EDWARD L. SNYDER, M.D., AND RONALD L. ELLISON, P.A.

ABSTRACT During coronary angioplasty, inflation of the balloon within the coronary artery produces transient arterial occlusion and frequently results in myocardial ischemia. Delivery of oxygenated autologous blood to the myocardium at risk during inflation may help mitigate this ischemia. Accordingly, we investigated the feasibility and safety of infusing blood through the central lumen of a dilatation catheter around the guidewire using both a model in vitro and clinical trials. In the tests in vitro, fresh blood was infused at flow rates up to 120 ml/min. Hemolysis was minimal at flow rates of 60 ml/min or less (≤0.92 ± 0.18%), but increased exponentially at higher rates (13.64 ± 2.37% at 120 ml/min, p<.002). A similar pattern was observed for potassium release. Platelet and leukocyte counts did not vary significantly, and β-thromboglobulin and muramidase remained at control levels. Although mean erythrocyte volume did not change, erythrocyte histograms and light microscopy demonstrated a subpopulation of red cell fragments averaging 25 to 40 fl in size at higher rates. A randomized, crossover clinical trial was next performed by delivery of blood perfusion at 60 ml/min to 15 patients undergoing coronary angioplasty. Levels of plasma hemoglobin, β-thromboglobulin, lactate dehydrogenase, and potassium remained constant before and after the perfusion and the control inflations. The maximum pain score was significantly lower with the perfusion inflation (4.1 ± 0.8 vs 6.0 ± 0.9, p<.003). Relative to baseline, the maximum ST segment elevation during the perfusion inflation (0.5 ± 0.3 mm) was nearly one-fourth that during the control inflation (1.9 ± 0.6 mm, p<.02). Thus, myocardial protection with oxygenated autologous blood perfusion at rates of 60 ml/min appears to be a safe and effective technique that may permit increased inflation time and extend the range of coronary angioplasty to include individuals at high risk for the procedure.


DESPITE THE INTERRUPTION of blood flow that occurs during balloon inflation, coronary angioplasty has proved to be generally well tolerated. However, recent research has uncovered the transient but profound physiologic disturbances that accompany the procedure, including ischemic pain, impairment of ventricular filling, electrical patterns of myocardial injury, and marked changes in regional contraction.1-6 Mitigation of these disturbances might improve patient tolerance and safety as well as broaden the applicability of the procedure.

Oxygen-carrying perfluorochemicals such as Fluosol-DA have been infused into the central lumen of a balloon dilatation catheter during inflation in an effort to lessen ischemia.7,8 Autologous oxygenated blood may represent a more suitable perfusate due to its superior oxygen delivery, higher carbon dioxide solubility, and lack of potential toxicity, but its use has been limited by concerns of hemolysis.9 Our study was designed to investigate, using both a model in vitro and clinical experiments, the feasibility and safety of autologous blood perfusion.

Methods

Trials in vitro. A model was constructed in vitro to directly assess blood damage at varying flow rates. Four new low-profile coronary balloon dilatation catheters (LPS 2530, USCI, Billerica, MA) and 0.014 inch (0.356 mm) diameter flexible steerable guidewires (USCI, Billerica, MA) were used, with the selection based on common usage within our catheterization laboratory. The guidewire was inserted into the central lumen, with the tip of the wire projecting 9 cm from the distal end. The...
distal end of the catheter was inserted into 2.90 mm internal diameter polyvinylchloride tubing (elastic modulus 16, 390 psi) to simulate a coronary artery. Fresh human blood was obtained from four healthy donors and was immediately anticoagulated with 2 units/ml heparin sodium.

All testing was done within 90 min of collection at 25°C. The blood was carefully placed in the syringe of an angiographic injector (Angiomat 3000, Liebel-Flarsheim, Cincinnati) calibrated earlier with graduated cylinders and a stopwatch. The catheter was connected to the injector via a high-pressure, large-bore, four-way stopcock to allow simultaneous and continuous recording of proximal catheter pressure. Pressure was measured with a strain-gauge transducer (Model AB, Data Instruments, Lexington, MA) with a 1% accuracy over a range of 0 to 500 psi.

After removal of a control sample ("0 ml/min"), the blood was injected at predetermined flow rates in 12 ml/min increments to a maximum of 120 ml/min.

**Blood sample analysis.** Samples of whole blood collected after infusion were analyzed for erythrocyte, leukocyte and platelet counts, total hemoglobin, and mean erythrocyte volume. Serum was used for determinations of potassium and lactate dehydrogenase concentrations. Wright-stained blood smears were inspected under light microscopy for the assessment of morphologic damage. Erythrocyte histograms were generated from each sample to assess variability in erythrocyte size.

Determination of platelet β-thromboglobulin release was performed with a radioimmunoassay as previously described. Samples were gently collected in chilled (4°C) plastic tubes containing theophylline and EDTA to inhibit granule release. Total β-thromboglobulin concentration in whole blood was assayed after platelet lysis with 1% Triton X-100. Plasma hemoglobin was determined spectrophotometrically by the oxidation of o-toluidine dihydrochloride. Muramidase was measured with a microbiologic-tubidimetric assay technique described previously.

Several values were derived from the assays described above. Potassium release represented the difference in serum potassium concentration between the sample collected during blood infusion and the control sample. Percent β-thromboglobulin release was defined as the plasma β-thromboglobulin concentration during blood infusion divided by the total β-thromboglobulin concentration, expressed as a percentage. Percent hemolysis was derived from the following equation:

\[
\frac{100 - (MEV \times EC \times 10^{-1})}{Hgb_p}\times Hgb_T
\]

where Hgb_p and Hgb_T represent plasma and total hemoglobin in grams per liter, respectively, MEV represents mean erythrocyte volume in femtoliters, and EC represents erythrocyte count x10^{12}/liter.

**Clinical trials.** After approval by the Human Studies Subcommittee of the Long Beach VA Medical Center, patients undergoing routine coronary angioplasty were enrolled if they satisfied the following criteria: (1) target lesion in the proximal or mid-portion of one of the three main coronary arteries, (2) no significant obstruction distal to the target lesion, (3) no baseline electrocardiographic abnormality that could interfere with the interpretation of myocardial ischemia, and (4) the absence of significant hypovolemia, hypoxemia, uncompensated heart failure, or active ischemia at the initiation of the procedure. Excluding oral secoarbital given 1 hr before the procedure, no medication was used that could interfere with pain perception. Supplemental oxygen was added as necessary to maintain a systemic arterial saturation at 90% or higher. A No. 9 femoral artery sheath with attached sidearm (USCI, Billerica, MA) was inserted and was used with a No. 8F guiding catheter to allow withdrawal of fully oxygenated blood from the sidearm after catheter placement. Systematic anticoagulation was accomplished with 10,000 units of heparin sodium.

**Protocol.** Angioplasty procedures were performed with USCI LPS balloon dilatation catheter systems with balloon diameters ranging from 2.0 to 3.5 mm, along with 0.014 inch (0.356 mm) diameter flexible steerable guidewires. The initial two balloon inflations were used for the protocol; one in which blood was infused through the catheter (perfusion inflation), and one in which it was not (control inflation). Each was performed at 6 atm pressure for 60 sec with no balloon repositioning between inflations. After successfully traversing the coronary lesion with the dilatation catheter, each patient was randomly assigned to either the perfusion inflation or control inflation first by use of a sealed envelope system. The patient was blinded to the order of the two inflations. With the use of radiolucent electrodes and leads, 12-lead electrocardiograms were obtained just before, during, and for 60 sec after each inflation at 12 sec intervals.

Maximum pain score during inflation was subjectively measured on a scale from 0 to 10, with 10 representing severe pain. Blood samples were obtained from a femoral venous sheath just before and 2 min after each balloon inflation. Each electrocardiogram was identified by a code number, and was later interpreted blindly and at random by an experienced electrocardiographer. ST segment deflection was measured at the J point in half-millimeter increments (1 mm = 0.1 mV). The maximum deflection in the leads corresponding to the target vessel (V_1 to V_6 for left anterior descending artery; II, III, and aVF for the right coronary artery; and I, aVL, and V_a for the circumflex artery) was recorded for further analysis. Measurement variability was assessed by random selection derived from a random number table of 10% of the electrocardiograms for reinterpretation. Mean intraobserver variability was 0.28 ± 0.6 mm, with a mean interobserver variability of 0.24 ± 0.05 mm.

**Perfusion technique.** Immediately before the perfusion inflation, 100 ml of oxygenated blood was withdrawn from the femoral arterial sheath sidearm into the prewarmed angiographic injector syringe containing 500 units heparin sodium. Coincident with balloon inflation, the blood was infused into the central lumen of the dilatation catheter around the guidewire at 60 ml/min. The infusion pressure was continually monitored with the high-pressure transducer described above. Immediately after completion of the inflation period, the blood remaining within the injector syringe was expelled and analyzed for temperature and oxygen saturation.

**Statistical analysis.** Group data are expressed as the mean ± SE. Means for continuous data are compared with two-tailed paired and unpaired Student's t tests where appropriate. Differences in categorical data are compared by Fisher's exact test. Infusion pressures and flow rates are correlated by least squares linear regression. A probability value of .05 was accepted as the limit of significance. Error bars on all graphs denote standard error.

**Results**

**Trials in vitro.** The results of the trials in vitro are listed in table 1. Predetermined flow rates ranging from 12 to 120 ml/min were used, along with control samples that were not subjected to infusion through the catheter ("0 ml/min"). The infusion pressure necessary to achieve a given flow rate varied little from catheter to catheter. Moreover, the relationship was quite linear
LEHMANN et al.

## TABLE 1
Results from catheter infusion trials in vitro

<table>
<thead>
<tr>
<th>Flow (mL/min)</th>
<th>Pressure (psi)</th>
<th>Total hemoglobin (g/l)</th>
<th>Plasma hemoglobin (g/l)</th>
<th>% Hemolysis (%)</th>
<th>Erythro (10¹⁰/l)</th>
<th>Leuko (10⁹/l)</th>
<th>Platelets (10⁹/l)</th>
<th>Erythro vol (fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>119 ± 7.5</td>
<td>0.4 ± 0.12</td>
<td>0.22 ± 0.07</td>
<td>4.04 ± 0.29</td>
<td>5.28 ± 0.34</td>
<td>172 ± 10</td>
<td>88.6 ± 0.7</td>
</tr>
<tr>
<td>12</td>
<td>31 ± 2.6</td>
<td>119 ± 6.9</td>
<td>0.4 ± 0.17</td>
<td>0.22 ± 0.09</td>
<td>4.06 ± 0.28</td>
<td>5.09 ± 0.17</td>
<td>165 ± 7</td>
<td>88.0 ± 1.9</td>
</tr>
<tr>
<td>24</td>
<td>63 ± 3.5</td>
<td>119 ± 7.5</td>
<td>0.3 ± 0.12</td>
<td>0.16 ± 0.04</td>
<td>4.05 ± 0.28</td>
<td>4.83 ± 0.14</td>
<td>178 ± 14</td>
<td>88.3 ± 1.9</td>
</tr>
<tr>
<td>36</td>
<td>95 ± 4.8</td>
<td>119 ± 6.9</td>
<td>0.6 ± 0.23</td>
<td>0.32 ± 0.13</td>
<td>4.07 ± 0.27</td>
<td>5.10 ± 0.23</td>
<td>170 ± 14</td>
<td>88.0 ± 1.8</td>
</tr>
<tr>
<td>48</td>
<td>127 ± 6.1</td>
<td>118 ± 7.5</td>
<td>0.5 ± 0.17</td>
<td>0.27 ± 0.09</td>
<td>4.04 ± 0.29</td>
<td>4.78 ± 0.21</td>
<td>174 ± 14</td>
<td>88.4 ± 2.0</td>
</tr>
<tr>
<td>60</td>
<td>162 ± 6.9</td>
<td>119 ± 7.5</td>
<td>1.7 ± 0.46</td>
<td>0.92 ± 0.18</td>
<td>4.03 ± 0.25</td>
<td>4.98 ± 0.36</td>
<td>180 ± 8</td>
<td>88.8 ± 2.3</td>
</tr>
<tr>
<td>72</td>
<td>194 ± 7.0</td>
<td>118 ± 7.5</td>
<td>3.7 ± 1.10</td>
<td>2.03 ± 0.43</td>
<td>4.00 ± 0.27</td>
<td>4.38 ± 0.33</td>
<td>194 ± 13</td>
<td>88.4 ± 2.0</td>
</tr>
<tr>
<td>84</td>
<td>231 ± 7.9</td>
<td>118 ± 7.5</td>
<td>6.8 ± 1.44</td>
<td>3.34 ± 0.51</td>
<td>3.96 ± 0.25</td>
<td>4.80 ± 0.26</td>
<td>205 ± 6</td>
<td>87.6 ± 1.6</td>
</tr>
<tr>
<td>96</td>
<td>264 ± 8.6</td>
<td>119 ± 7.5</td>
<td>10.9 ± 2.25</td>
<td>6.04 ± 1.38</td>
<td>3.87 ± 0.25</td>
<td>4.33 ± 0.33</td>
<td>217 ± 14</td>
<td>88.1 ± 2.0</td>
</tr>
<tr>
<td>108</td>
<td>296 ± 9.3</td>
<td>119 ± 7.5</td>
<td>15.3 ± 2.71</td>
<td>8.61 ± 1.96</td>
<td>3.75 ± 0.23</td>
<td>4.78 ± 0.14</td>
<td>242 ± 25</td>
<td>88.1 ± 2.0</td>
</tr>
<tr>
<td>120</td>
<td>332 ± 9.3</td>
<td>118 ± 7.5</td>
<td>23.5 ± 2.13</td>
<td>13.64 ± 2.37</td>
<td>3.57 ± 0.20</td>
<td>4.88 ± 0.21</td>
<td>249 ± 55</td>
<td>88.2 ± 1.8</td>
</tr>
</tbody>
</table>

Values are means ± SE for four trials (B-TG and Muramidase values are from one trial).

B-TG = plasma β-thromboglobulin; %B-TG = plasma β-thromboglobulin expressed as a percentage of the total in whole blood; Erythro = erythrocyte count; Erythro vol = mean erythrocyte volume; LDH = lactate dehydrogenase; Leuko = leukocyte count; Platelets = platelet count; psi = pounds per square inch.

over the range tested, as evidenced by the resulting correlation coefficient of .999 (figure 1). This suggests that Poiseuillian flow characteristics predominate, and that infusion pressures can be accurately predicted for any given flow.

**Extent of hemolysis.** Hemolysis was assessed by quantitation of hemoglobin release from red cells into the surrounding plasma during catheter infusion. Figure 2 demonstrates that minimal plasma hemoglobin, indicated by the darkly shaded area, was present at the lower flow rates. However, at rates in excess of 60 ml/min, the amount of plasma hemoglobin increased sharply. The percent hemolysis for each flow rate was also computed with the results graphically depicted in figure 3. As shown, the percent hemolysis remained below 1% for flows of 60 ml/min or less. Greater flows resulted in an exponential increase in hemolysis to a maximum of 13.64 ± 2.37% at 120 ml/min.

---

**FIGURE 1.** Relationship between infusion pressure and blood flow. Values represent means of four trials. Results for linear regression analysis (line not shown) include r = .999, SEE = 1.78, slope = 2.80 ± 0.01, intercept = 1.51 ± 0.90, p<.0001.
Quantitation of formed blood elements. The influence of flow rate on the numbers of formed elements in the blood collected after catheter infusion is shown in figure 4. The number of erythrocytes present remained stable at low flows, but decreased significantly at flows of 120 ml/min (p<.05). Total leukocyte counts demonstrated more variability but no significant trend. Moreover, neither granulocyte nor lymphocyte counts changed over the range of flow rates studied. Platelet counts also demonstrated no statistically significant change with increasing flow rates.

Enzyme, protein, and electrolyte release. Quantitation of the release of substances normally concentrated in formed blood elements was used to provide a more sensitive index of blood damage. Levels of lactate dehydrogenase remained normal (1.67-3.75 ukat/liter) until flow exceeded 72 ml/min (table 1); greater flows resulted in considerable release of lactate dehydrogenase. Potassium release is a potentially important variable, not only for estimation of blood damage, but also because a significant release could raise serum potassium to a level sufficient to promote or induce arrhythmias. Potassium release was measured at 0.58 ± 0.25 mmol/liter for flows of 60 ml/min, increasing to 5.58 ± 1.04 mmol/liter for flows of 120 ml/min. At flow rates of 60 ml/min or less, the plasma concentration of the platelet-specific protein β-thromboglobulin was similar to the control value and did not exceed 1% of the total amount contained within whole blood (table 1). The plasma level of muramidase, normally concentrated in neutrophils, remained at control levels at all flow rates tested, suggesting minimal neutrophil activation or lysis.

Erythrocyte morphology. Although erythrocyte damage...
gauged by plasma hemoglobin was limited to high flow rates (figure 2), more subtle morphologic changes that would not be detected by the tests reported above might occur at lower flow rates. Mean erythrocyte volume did not change (table 1), but this does not exclude the possible formation of a small subpopulation of cells of altered size. By displaying the frequency of erythrocytes relative to their volume, erythrocyte

FIGURE 4. Counts of erythrocytes, leukocytes, and platelets in blood infused in vitro at varying flow rates. Points represent means ± SE. Only erythrocyte counts varied significantly (p<.05). The apparent increase in platelet counts at the highest flow rates resulted from inclusion of occasional erythrocyte fragments of a similar size during the automated counting procedure (verified by light microscopy).

FIGURE 3. Effect of flow rate in vitro on percent hemolysis. Points represent mean values ± SE for four trials.
histograms are able to detect such subpopulations. As shown in figure 5, the histograms for this representative subject appeared normal at flow rates of 84 ml/min or less, with a small subpopulation of cells averaging 25 to 40 fl in size appearing at higher rates. Light microscopy of Wright smears confirmed these to be erythrocyte fragments (figure 6).

Clinical trials

Patient characteristics. Of the 15 patients entering the protocol, the vessel dilated was the left anterior descending artery in 11, the right coronary artery in three, and the circumflex artery in one. The target lesion was located in the proximal portion of the artery in 10 patients (67%) and in the mid portion in the remainder (33%). The percent diameter reduction gauged by visual inspection and caliper measurements averaged 86 ± 8% (range 70% to 96%). Two patients (13%) had evidence of a prior myocardial infarction in the distribution of the target artery as gauged by pathologic Q waves on 12-lead electrocardiography or regional dyssnergy during contrast ventriculography.

None had visible collaterals supplying the target artery. All target lesions were successfully dilated (residual stenosis ≤40%).

Protocol. Randomization resulted in the performance of the perfusion inflation first in seven patients and the control inflation first in eight patients. The mean infusion pressure required to maintain a 60 ml/min flow rate through the catheter was 189 ± 6 psi. Temperature of the blood used for perfusion averaged 33.0 ± 0.2°C. This likely represents a slight underestimate of true perfusate temperature since it ignores both the time delay between the perfusion inflation and temperature measurement, and the warming that occurs during passage of the perfusate through the intravascular portion of the catheter.

Comparison of perfusion and control inflations. The extent of blood damage was assessed by measurement of plasma hemoglobin, β-thromboglobulin, lactate dehydrogenase, and serum potassium in systemic venous blood collected before and after each inflation. As shown in table 2, there were no significant differences in any of these values.

Table 3 lists pain severity and electrocardiographic changes that occurred during the protocol. Of the 13 patients (87%) who experienced ischemic-type pain during balloon inflations, 11 reported less pain with the perfusion inflation compared with the control inflation, and two reported equal pain severity with the two inflations. In no patient was the pain greater during the perfusion than during the control inflation. Overall, the mean maximum pain score was significantly less (p<.003) with the perfusion inflation (4.1 ± 0.8) than with the control inflation (6.0 ± 0.9).

All patients exhibited ST segment elevation overlying the area of the heart supplied by the target artery during balloon dilatation. The temporal course of the ST segment changes are graphically depicted in figure 7. Mild ST segment elevation occurred in eight (53%) patients after crossing the lesion with the dilatation catheter but before inflation, presumably due to further impairment of already compromised blood flow. After 36 sec of dilatation, the ST segments during the control inflation were significantly higher than during the perfusion inflation. As shown in table 3, the maximum change in ST segment elevation was nearly fourfold greater in the control group (p<.02). Of the patients with ST segment elevation before balloon inflation, 60% demonstrated an actual improvement relative to this baseline elevation during the perfusion inflation.

During the 60 sec of balloon expansion, the heart rate increased 4.8 ± 2.1% with the control inflation but actually decreased 3.3 ± 1.2% with the perfusion

![FIGURE 5. Erythrocyte histograms from samples of blood infused in vitro in one trial. The distribution of erythrocyte volumes remains constant at all flow rates except for a limited number of small cells (arrow) that appear at rates greater than 96 ml/min. Light microscopy confirms these to be erythrocyte fragments. The secondary peak at 175 fl seen in each histogram is produced artifactually from double counting of cells.](http://circ.ahajournals.org/)

Vol. 76, No. 2, August 1987
FIGURE 6. For legend see opposite page.
inflation. This small but statistically highly significant difference (p<.001) might be explained by pain-induced enhancement of sympathetic tone accompanying the control inflation, or by less well-defined hemo-
dynamic changes occurring during the inflations. During and after balloon expansion, arrhythmias were uncommon. Three patients experienced arrhyth-
mas with the control inflation (ventricular premature beats (VPBs) >10/min in one, transient atrial flutter in one, and nonsustained ventricular tachycardia in one). One patient experienced an arrhythmia with the perfusion inflation (VPBs >10/min). The small numbers involved preclude statistical significance.

Discussion

The need for myocardial protection. During coronary angioplasty, balloon inflation results in total coronary artery occlusion. An obvious possible sequel of this is transient myocardial ischemia. Although concern for this possibility was expressed over a decade ago by the creator of the procedure,1 widely accepted clinical application of angioplasty has shown it to be generally well tolerated.

Several recent developments in the field have reestab-
lished the desirability of ischemia abatement during angioplasty. First, it is now well recognized that profound myocardial dysfunction regularly accompanies balloon inflation.1,2,4 Numerous hemodynamic and mechanical variables have been shown to be transiently but markedly disturbed during dilation. With 60 sec of inflation, previous investigators have documented a mean decrease in ejection fraction from 61% to 48%,1 and a mean increase in left ventricular end-diastolic pressure from 16 to 30 mm Hg.2 The new onset of regional akinesia or dyskinesia during inflation is apparent in nearly all patients assessed by two-dimen-
sional echocardiography.4

Second, there has been a recent trend in clinical angioplasty toward more prolonged inflation times. Experimental evidence suggests that this may improve initial stenosis reduction,13 and inflation periods of up to 10 min are now being used in some laboratories.14 It has been shown in experimental animals15-17 and in clinical trials1,2,4 that hemodynamic and mechanical changes occur shortly after coronary occlusion, typically within 20 sec.1,2,4 Restoration of flow reverses this ventricular impairment, but only if the ischemic period is short. In dogs, ischemia of greater than 5 min duration can delay functional recovery for up to 6 hr,16 with repeated 5 min episodes of occlusion producing actual myocardial necrosis.18 Prompt recovery of systolic function is regularly found in patients exposed to the brief (≤60 sec) periods of ischemia encountered during angioplasty. However, more subtle indexes of diastolic function, such as the regional constant of elastic stiffness, can remain abnormal for more than 12 min after completion of a standard angioplasty procedure.3

Third, the role of angioplasty in the treatment of coronary disease has expanded to include medically unstable patients with multivessel disease and severe proximal stenoses. Unprotected dilatation in this group may prove to be especially risky. Myocardial protection may allow the application of angioplasty to sub-
groups of patients in whom it was not often attempted in the past, such as those with left main coronary disease.

The feasibility of blood as a perfusate. The ischemia associated with transient arterial occlusion during coronary angioplasty might be lessened or eliminated by delivery of an oxygen-rich perfusate to the jeopard-
dized myocardial bed during balloon inflation. Autolo-
guous oxygenated blood represents a logical choice of perfusate, with delivery accomplished by infusion.
TABLE 3
Symptoms and electrocardiographic results from clinical trials

<table>
<thead>
<tr>
<th></th>
<th>Perfusion inflation</th>
<th>Control inflation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum pain score</td>
<td>4.1 ± 0.8</td>
<td>6.0 ± 0.9</td>
<td>&lt;.003</td>
</tr>
<tr>
<td>Δ ST segment (mm)</td>
<td>0.5 ± 0.3</td>
<td>1.9 ± 0.6</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Δ Heart rate (%)</td>
<td>-3.3 ± 1.2</td>
<td>+4.8 ± 2.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. with arrhythmias</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. Δ Heart rate = change in heart rate between initiation and termination of balloon inflation (60 sec) expressed as a percentage; Δ ST segment = change in ST segment between initiation and termination of inflation (60 sec).

through the central lumen of a dilatation catheter. However, there are several potential difficulties with this approach.

One primary concern is that the high pressures required to maintain physiologic flow rates through the narrow catheter might cause significant damage to the formed blood elements. The high hydraulic resistance of our catheter system results from the intrinsically small size of the central lumen further narrowed by the presence of the guidewire (minimal effective cross-sectional area = 0.103 mm²). Maintenance of a flow rate of 60 ml/min results in a mean exit velocity of perfusate of 970 cm/sec. Our data reveal that erythrocytes sustained minimal acute damage at this flow rate despite the high velocities encountered. Higher flow rates produced an exponential increase in hemolysis.

These results are consistent with prior experimental work investigating modes of mechanical erythrocyte damage. Hemolysis can occur from cell/catheter wall interaction, but the laminar flow characteristics (Reynolds number << 2000), the brief period of contact, and the smooth internal surface of our catheter system all serve to minimize this effect. In-bulk lysis of erythrocytes unrelated to wall interactions has also been documented and can occur at a relatively modest shear stress of 1000 dynes/cm² if applied for several minutes. This process is also unlikely to be contributory in our system in which the erythrocyte transit time through the narrow portion of the catheter lumen averages only 4.3 msec. A final form of hemolysis can be found only above a shear stress threshold of 40,000 dynes/cm² and occurs when the yield strength of the membrane is exceeded. In this high-stress regimen, erythrocyte exposure time required for lethal damage is quite short, averaging 10⁻⁵ sec. Models for investigating this process have frequently used high-velocity fluid jets injected into a reservoir of stationary blood, a situation somewhat analogous to our perfusion system. Forstrom had found negligible hemolysis at jet velocities below 1700 cm/sec, with an exponential increase in blood damage for greater velocities. These
data are remarkably similar to empirically derived hemolysis rates determined from our trials in vitro, and supports the concept that blood damage in our system is predominantly due to this "jet effect."

Although our data suggest tolerably low levels of hemolysis at perfusion rates of 60 ml/min or less, other concerns regarding blood damage remain. For example, platelets and granulocytes contain a number of hemostatically active substances that might be released by cell lysis or activation during transit through the dilatation catheter. This could promote a thrombotic milieu "downstream" and possibly result in thrombus formation in the distal artery. In our trials in vitro, neither leukocyte nor platelet counts decreased over the range of perfusion rates used. In addition, muramidase and \( \beta \)-thromboglobulin, a known inhibitor of heparin,\(^{24} \) remained at control levels for flow rates of 60 ml/min or less. These data are in concert with the findings of Johnston et al.,\(^{25} \) who reported that platelets subjected to very high stresses (10\(^2\) to 10\(^3\) dynes cm\(^{-2}\)) for short exposure times (10\(^{-5}\) sec) were more resistant to stress lysis than were erythrocytes. In our clinical trials, no angiographically demonstrable thrombi were evident at either the site of balloon inflation or the distal artery.

Significant potassium release from erythrocytes during catheter perfusion could promote electrical instability in the distal myocardial bed. Seeman et al.\(^{26} \) have found that potassium ions escape from sublethally damaged erythrocytes long before hemoglobin release occurs. Indeed, flow rates of 120 ml/min in our trials in vitro resulted in a marked increase in potassium concentration of 5.58 \( \pm \) 1.04 mmol/liter. The release of potassium occurring at flow rates used in our clinical trials (60 ml/min) was one-tenth that amount and would not be expected to enhance electrical instability. The results of electrocardiographic monitoring lend further reassurance, since there was a statistically insignificant trend toward fewer arrhythmias during the perfusion inflation than during the control inflation, possibly due to a reduction in myocardial ischemia.

The nonphysiologic infusion pressures required to maintain adequate flow rates might produce considerable vascular damage if transmitted directly to the myocardial capillary bed. Although lower pressures could be achieved by removal of the guidewire before infusion,\(^{27} \) we believe this would pose an unwarranted clinical risk. Two factors help minimize the possibility of vascular damage. First, the hydraulic resistance of the catheter system used with the guidewire in place (1.12 \( \times \) 10\(^7\) dynes sec cm\(^{-5}\)) is 100-fold greater than the portion of the myocardial bed distal to an epicardial artery (\( \sim 1 \times 10^5 \) dynes sec cm\(^{-5}\)),\(^{28} \) so that 99\% of the pressure drop occurs within the catheter itself, and coronary arterial pressures remain in the physiologic range. Second, we carefully excluded from our clinical trials any patient with significant obstructions distal to the target lesion. If a significant impediment to epicardial coronary artery flow did exist, however, once the rising intracoronary pressure exceeded that of the inflated balloon (typically 3 to 10 atm), the excessive pressure would likely be relieved by balloon collapse long before coronary artery rupture could occur.

The final issue of safety involves the mechanical effect of the infused blood on the target artery when subjected to the high exit flow velocities required to maintain physiologic rates of flow. It would obviously be detrimental if the blood stream exiting the catheter were of sufficient force to disrupt a neighboring atherosclerotic plaque or induce an intimal tear. Although at 60 ml/min the mean exit velocity of the infused blood is considerable (970 cm/sec), the maximum force generated by the jet is small (1020 dynes) due to the low flow rates involved.\(^{29} \) In our model in vitro, the infused blood could be seen to track along the guidewire and dissipate within several millimeters of its exit from the catheter tip. Moreover, neither coronary occlusion nor dissection has been observed by us or by others during perfusion around the guidewire using other perfusates at identical flow rates.\(^{7, 8, 30} \)

Experimental blood perfusion during angioplasty has been performed in dogs\(^{31, 32} \) and pigs\(^{33} \) for inflation periods of up to 2 hr, with improvements noted in ST segment changes, frequency of ventricular fibrillation, and myocardial histology. Preliminary results for two studies in humans have also been reported. Angelini et al.\(^{27} \) found distal hemoperfusion to be helpful in suppressing clinical manifestations of ischemia in three patients. Timmis et al.\(^{34} \) also noted a reduction in echocardiographic dyssnergy. Although these results are encouraging, investigators in both of these studies chose to remove the angioplasty guidewire before perfusion, making direct comparison with the current study difficult.

**The use of alternative perfusates.** Other oxygen-carrying substances have been proposed as an alternative to blood for myocardial protection during angioplasty. Most clinical work for this particular application has used Fluosol-DA 20% (Alpha Therapeutic Corporation), a perfluorochemical emulsion capable of high oxygen solubility.\(^{35, 36} \) Experiments in animals\(^{37} \) and in humans\(^{7} \) have demonstrated a reduction in ischemic manifestations with this agent. Using two-dimensional echocardiography during clinical angioplasty, Clement

---

Vol. 76, No. 2, August 1987
et al. recently found that Fluosol-DA 20% infused at 60 ml/min was capable of preventing the marked regional wall motion abnormalities that regularly accompanied unprotected balloon inflations.

A comparison of Fluosol-DA 20% and blood reveals several significant disadvantages of the artificial perfusate. First, at a given flow rate or infusion pressure, both oxygen content and tissue delivery are much less than those with blood. In maintaining a normal basal myocardial oxygen tension of 20 mm Hg, artificially hyperoxygenated Fluosol-DA 20% (PO₂ = 550 mm Hg) can provide only a third as much oxygen as physiologically oxygenated blood (PO₂ = 100 mm Hg). Second, carbon dioxide solubility of Fluosol-DA 20% is only one-eighth that of blood, increasing the chance of suboptimal clearance in borderline flow states. Third, hepatic toxicity has been encountered during prior clinical trials of Fluosol-DA 20%. Finally, the inconveniences of solubilization and oxygenation and the additional cost of Fluosol-DA 20% favor the use of autologous blood.

Some of these factors may account for the favorable responses of arrhythmias, chest pain, and electrocardiographic changes in the present investigation relative to prior clinical Fluosol perfusion studies. Moreover, a direct comparison of the two perfusates in dogs has recently been reported; Tokioka et al. found that only blood perfusion was capable of preventing the regional systolic dysfunction, ST elevation, and altered lactate extraction that result from transient coronary arterial occlusion.

Clinical applicability. This study demonstrates that oxygenated blood can be successfully infused through the central lumen of a dilatation catheter around the guidewire. This can be accomplished easily and safely with standard equipment available in most catheterization laboratories. Although the extent of hemolysis is substantial at flow rates approaching 120 ml/min, rates of 60 ml/min or less in the dilatation catheter system used still provide physiologic blood flow but are not associated with significant hemolysis, potassium release, alteration of erythrocyte morphology, or activation or lysis of platelets and leukocytes. Feasibility testing in patients has shown that myocardial perfusion with oxygenated autologous blood reduces the pain and ST segment changes associated with coronary angioplasty without promoting vascular damage or electrical instability. This new technique may allow the extension of angioplasty to subgroups of patients and lesions not previously approachable, and may permit more complete revascularization through longer balloon inflation times. However, further efficacy testing is warranted in other catheter systems before blood perfusion can be routinely recommended during coronary angioplasty.

We gratefully acknowledge the assistance of Dr. Carl Jaffe, the editorial advice of Drs. Victor Froelicher, Robert Detrano, and Kern Guppy, the laboratory support of Paula Napyanch and Michael Osaki, and the secretarial assistance of Mona Risch.

References
17. Theroux P, Franklin D, Ross J Jr, Kemper WS: Regional myocardial function during acute coronary artery occlusion and its modifi-
cation by pharmacologic agents in the dog. Circ Res 35: 896, 1974
34. Timmis AD, Crick JCP, Phil D, Griffin B, Sowton E: Arterial blood infusion for myocardial protection during PTCA. J Am Coll Cardiol 7; 105A, 1986
Autologous blood perfusion for myocardial protection during coronary angioplasty: a feasibility study.
K G Lehmann, J E Atwood, E L Snyder and R L Ellison

Circulation. 1987;76:312-323
doi: 10.1161/01.CIR.76.2.312

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/76/2/312

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/