Effects of Perfluorochemical Hemodilution on Coronary Blood Flow Distribution in Dogs

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To determine the effect of perfluorocarbon (PFC) hemodilution on myocardial vessel capacity to autoregulate, circumflex coronary artery pressure-flow relations were studied in anesthetized dogs under three conditions: maximal vasodilatation before and after PFC; autoregulation before and after PFC with 100% oxygen supplemented with room air ventilation, and autoregulation with PFC hemodilution during either room air or 100% oxygen supplemented with room air ventilation. During coronary vasodilatation, PFC did not modify coronary conductance or zero-flow pressure. During autoregulation after PFC, the lower pressure limit of the autoregulatory pressure-flow relation was shifted leftward. This leftward shift occurred because endocardial blood flow was maintained at a lower coronary perfusion pressure with PFC while epicardial blood flow was unchanged. Endocardial blood flow was also preserved at 50% of control blood flow levels as evidenced by the higher endocardial-epicardial blood flow ratio with PFC. After PFC with 100% oxygen supplemented with room air ventilation, oxygen transport increased significantly when coronary perfusion pressure was below the lower pressure limit; the effect was most prominent in the endocardial tissue layer. Thus, PFC shifts the lower pressure limit to the left because of the increased ability of the endocardial vessel to autoregulate. Consequently, PFC can be considered a useful intervention for improving endocardial oxygen transport at low coronary perfusion pressures. (Circulation 1988;78:746-753)

Coronary blood flow is maintained over a wide range of coronary perfusion pressures for a given myocardial metabolic demand because of the capacity of the myocardial vessel to autoregulate. At a certain point of the autoregulatory process, coronary blood flow decreases with further reductions in coronary perfusion pressure. This point has been defined as the lower pressure limit of the autoregulatory pressure-flow curve (LPL) by Klocke et al. These investigators have also shown that the steady-state pressure-flow relation is likely to be shifted upward and to the right with increases in myocardial oxygen demand. Pressure-flow relations vary in the different myocardial layers. The LPL of the endocardial tissue layer is higher than that of the epicardium. Interventions that modify blood viscosity or myocardial oxygen demand may be expected to produce changes mostly in the LPL of the endocardial tissue layer.

Perfluorochemical emulsions are of potential medical interest because of their ability to transport oxygen in solution without hemoglobin, which acts as the oxygen carrier. Fluosol-DA (20%) (PFC) has been found useful as red blood cell substitutes for maintenance of intravascular volume in animals and patients. However, the effects of PFC hemodilution on myocardial blood flow, oxygen transport, and regional blood flow distribution in the heart during maintained autoregulation and on coronary “back pressure” and vascular conductance during vasodilatation have not been examined. Such studies may be relevant to determine whether myocardial oxygen transport can be improved and whether coronary back pressure and vascular conductance are affected during PFC hemodilution.

If the ability of the endocardial vessel to autoregulate increases after PFC hemodilution, we would expect a leftward shift of the LPL, which would result in increased oxygen transport in the endocardial tissue layer. This would have clinical implications during reduced coronary perfusion pressure. The present study was undertaken to test this hypothesis.
Materials and Methods

**Animal Preparation**

Adult, male mongrel dogs (body weight, 25–40 kg) were pretreated with cortisone acetate (Cortone, 4 mg/kg i.m.) 12 hours before the experiments to minimize possible adverse reactions to PFC administration. Dogs were premedicated with diazepam (1 mg/kg i.v.) and fentanyl (20 μg/kg i.v.) and anesthetized with α-chloralose (75 mg/kg i.v.). α-Chloralose spares both autonomic reflexes and renal function in dogs, and its effect on cardiac function has been examined. Dogs were endotracheally intubated and ventilated by a positive-pressure respirator. Arterial blood gases were monitored throughout the study, and respiratory settings were adjusted to maintain PO2 and PCO2 within the physiological range.

Polyethylene catheters (8F) were positioned in the femoral veins for administration of drugs and fluids, and hydrocortisone sodium succinate (Solu-Cortef, 10 mg/kg i.v.) was administered. A splenectomy was performed through a midline abdominal incision to eliminate alterations in blood volume and hematocrit levels during the experiment. Body temperature was measured with a thermistor probe positioned in the abdomen and maintained at 37–39°C with heating pads. The chest was entered through a left thoracotomy in the fifth intercostal space, the pericardium was opened, and the heart was supported in a pericardial cradle. The proximal 4 cm of the circumflex coronary artery was dissected, and an electromagnetic flow probe connected to a flowmeter (Narcomatic Instruments, Houston, Texas) was positioned to monitor circumflex artery blood flow. A micrometric occluder was placed distal to the flow transducer to control coronary perfusion pressure. Circumflex artery pressure distal to the micrometric occluder was measured with a small caliber (No. 22 intracath) fluid-filled catheter. Dogs were initially given sodium heparin (100 units/kg i.v.) and subsequently every hour during the experiment. A catheter (5F) was inserted distally into the coronary sinus to obtain coronary sinus pressure and for withdrawal of coronary sinus blood samples to enable determination of overall metabolic status of the left ventricle. Systemic pressures were measured in the ascending aorta with a pigtail catheter (8F) passed retrogradely from the right femoral artery. A Konigsberg P-7 high-sensitivity pressure transducer (Pasadena, California) was secured in the left ventricle through an apical stab wound for measurement of left ventricular pressure. Catheters (8F) were inserted into the left atrium to measure pressure and for injection of radiolabeled microspheres. A catheter (8F) was positioned in the internal thoracic artery for withdrawal of reference blood samples for myocardial blood flow analysis.

Left atrial, distal left circumflex artery, coronary sinus, and ascending aorta fluid-filled catheters were connected to Statham P23DB (Gould-Statham, Cleveland, Ohio) strain gauge manometers; zero was set at midchest level. The Konigsberg pressure gauge was cross-calibrated with measurements of systolic aortic and diastolic left atrial pressures. Hemodynamic measurements, circumflex artery blood flow, and lead II electrocardiogram were recorded on a multichannel Electronics for Medicine recorder (Montreal, Canada).

**Protocol**

Circumflex artery pressure-flow relations were constructed with blood flow data obtained with the electromagnetic flow probe and diastolic circumflex pressure during three periods: 1) maximal vasodilatation before and with PFC hemodilution with 100% oxygen supplemented with room air ventilation, 2) maintained autoregulation with 100% oxygen supplemented with room air ventilation before and with PFC hemodilution, and 3) maintained autoregulation initially with 100% oxygen supplemented with room air ventilation and then room air ventilation after PFC hemodilution. One liter of PFC emulsion was administered intravenously at a rate of 25 ml/min during these experiments. Systemic hemodynamics and arterial blood gases were measured before and after PFC hemodilution. Dogs in group A received adenosine (4.7 μM) intra-atrially (infusion rate of 1.0 ml/min) to abolish reactive hyperemia.

During maximal vasodilatation (group A) circumflex artery pressure-flow relations before and after PFC hemodilution were initially measured with the electromagnetic flow probe. Thereafter, each pressure-flow relation was repeated, and radiolabeled microspheres were injected at four points, at stable state, which corresponds to 100% (i.e., control), 75%, 50%, and 25% of mean coronary blood flow. At each of these blood flow levels, no reactive hyperemic response was observed.

During maintained autoregulation (group B), circumflex artery pressure-flow relations before and after PFC hemodilution were initially measured with the electromagnetic flow probe. Thereafter, each autoregulatory pressure-flow relation was repeated, and radiolabeled microspheres were injected before and after PFC hemodilution at four points on the coronary pressure-flow relation: at control coronary blood flow, at the LPL, at the coronary perfusion pressure that produced a coronary blood flow level at 75%, and at 50% of control circumflex artery blood flow. Dogs in groups A and B were ventilated with 100% oxygen supplemented with room air throughout the experiment to increase the oxygen carrying capacity of the PFC emulsion.

Circumflex artery pressure-flow relations in group C dogs were obtained after PFC hemodilution as described in group B dogs; however, these dogs were ventilated with either room air or with 100% oxygen supplemented with room air to evaluate the emulsifier and the oxygen-carrying capacity effects of PFC.
Regional myocardial blood flow was determined with radiolabeled microspheres (15 μm) as previously described.18,19 The purpose of the microsphere injections was to determine PFC-induced alterations in myocardial blood flow distribution of the left circumflex artery perfusion bed.

Arterial and coronary sinus blood samples were withdrawn immediately after microsphere injection for determination of \(P_O_2\), \(P_C_0_2\), pH, hematocrit level, fluorocrit level (i.e., relative volume of packed PFC particles/100 ml blood), hemoglobin levels, and percent oxygen saturation. The \(O_2\) content of arterial and coronary sinus blood samples was determined with a Lex-O2-Con K apparatus (Lexington Instruments, Lexington, Massachusetts). Myocardial oxygen consumption (ml/min/100 g) was calculated as the product of total coronary blood flow measured with microspheres (ml/min/100 g) and the arterocoronary sinus oxygen content (ml/ml) difference. Oxygen transport (ml/min/100 g) was calculated as the product of arterial oxygen content (ml/ml) and endocardial or epicardial blood flow (ml/min/100 g). Blood samples were also obtained for arterial and coronary sinus lactate measurements in dogs with maintained autoregulation. Lactate was determined as previously described,20 and percent lactate extraction was calculated as the quotient of the arterocoronary sinus differences and arterial lactate measurements.

At the end of each experiment, India ink was injected into the left circumflex artery to define the posterior perfusion bed, and simultaneously the heart was arrested by injecting a saturated potassium chloride solution into the left atrium. The hearts were excised, washed, and subsequently fixed by immersion in 10% (w/v) neutral formalin. The atria, ventricles, and septum were sectioned as previously reported by Rouleau et al.4 Regional myocardial flow to the left ventricle was calculated with a least-squares fit method.19

**Data Analysis**

Hemodynamic and metabolic data for the different experimental groups were compared by an unpaired Student’s t test21 and ANOVA. Two-way analysis of variance with replication22 was used to evaluate the effect of PFC treatment on coronary blood flow and myocardial oxygen transport at different coronary perfusion pressure levels. Regional myocardial blood flow and oxygen consumption changes were assessed by single factor ANOVA at four different coronary perfusion pressures, and differences in blood flow within myocardial tissue layers were assessed by Newman-Keuls multiple range tests.

All data are expressed as the mean ± SD, and a probability of less than or equal to 0.05 was considered to be statistically significant.

**Results**

Experiments were performed on 24 dogs for this study. Eight dogs were excluded because acute congestive heart failure (n = 4) or severe hypotension (n = 4) occurred after PFC administration. Data from the remaining 16 dogs provide the basis for this study.

**Cardiac Hemodynamic Data**

Hemodynamic and blood gas measurements for group A dogs (n = 6) were made before vasodilatation and before PFC hemodilution as shown in Table 1. After vasodilatation, heart rate increased (\(p < 0.05\)) and left ventricular (LV) systolic pressure decreased (\(p < 0.05\)); however, LV end-diastolic and mean coronary sinus pressures were unchanged. Administration of PFC decreased the hematocrit level from 40 to 31 vol%, whereas other measurements remained unchanged.

In group B dogs (n = 5) with PFC hemodilution, heart rate increased (\(p < 0.05\)), whereas LV systolic

**Table 1. Hemodynamic and Blood Gas Data**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>HR (beats/min)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>PCS (ml/min/100 g)</th>
<th>RPP (mm Hg)</th>
<th>Hct (%)</th>
<th>(P_O_2) (mm Hg)</th>
<th>(P_C_0_2) (mm Hg)</th>
<th>pH</th>
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<td>Vasodilatation</td>
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<tr>
<td>Before vasodilatation</td>
<td>6</td>
<td>115 ± 24</td>
<td>142 ± 12</td>
<td>12 ± 6</td>
<td>10 ± 7</td>
<td>16.8 ± 4.0</td>
<td>45 ± 4</td>
<td>266 ± 118</td>
<td>38 ± 3</td>
<td>7.40 ± 0.03</td>
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<tr>
<td>Control O2</td>
<td>5</td>
<td>143 ± 12†</td>
<td>108 ± 8</td>
<td>7 ± 3</td>
<td>8 ± 4</td>
<td>15.6 ± 1.7</td>
<td>35 ± 8</td>
<td>323 ± 89</td>
<td>37 ± 6</td>
<td>7.43 ± 0.05</td>
</tr>
<tr>
<td>PFC O2</td>
<td>5</td>
<td>143 ± 12‡</td>
<td>108 ± 8</td>
<td>7 ± 3</td>
<td>8 ± 4</td>
<td>15.6 ± 1.7</td>
<td>35 ± 8</td>
<td>323 ± 89</td>
<td>37 ± 6</td>
<td>7.43 ± 0.05</td>
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<td>Autoregulation</td>
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</tr>
<tr>
<td>Control O2</td>
<td>5</td>
<td>144 ± 30</td>
<td>114 ± 27</td>
<td>8 ± 4</td>
<td>9 ± 5</td>
<td>15.9 ± 3.2</td>
<td>35 ± 9</td>
<td>82 ± 28</td>
<td>28 ± 8</td>
<td>7.42 ± 0.04</td>
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<tr>
<td>PFC O2</td>
<td>5</td>
<td>132 ± 33</td>
<td>125 ± 23</td>
<td>11 ± 4</td>
<td>8 ± 5</td>
<td>16.1 ± 3.3</td>
<td>38 ± 9</td>
<td>366 ± 67§</td>
<td>38 ± 6</td>
<td>7.43 ± 0.05</td>
</tr>
</tbody>
</table>

All values are mean ± SD; n, number of dogs studied.

HR, heart rate (beats/min); LVSP, systolic left ventricular pressure (mm Hg); LVEDP, left ventricular end-diastolic pressure (mm Hg); PCS, mean coronary sinus pressure (mm Hg); RPP, rate-pressure product (beats/min × mm Hg × 10⁻³); Hct, hematocrit (vol %); Fct, fluorocrit (vol %); \(P_O_2\), arterial oxygen tension (mm Hg); \(P_C_0_2\), arterial carbon dioxide tension (mm Hg). Control O2, no perfluorocarbon (PFC) hemodilution with 100% oxygen supplemented with room air ventilation; PFC O2, PFC hemodilution with 100% \(O_2\) ventilation.

\(*p < 0.05\) vs. before adenosine; \(\dagger p < 0.05\) vs. control O2; \(\ddagger p < 0.05\) vs. control O2; \(§ p < 0.001\) vs. PFC RA. Intergroup statistical comparison of data by unpaired Student’s t tests and one-way ANOVA.
pressure decreased (p<0.05). However, the rate-pressure product, and LV end-diastolic and mean coronary sinus pressures were unchanged.

In group C dogs (n=5) with PFC hemodilution during room air or 100% oxygen supplemented with room air ventilation, heart rate, LV systolic pressure, rate-pressure product, LV end-diastolic and mean coronary sinus pressures, hematocrit level, fluorocrit level, and arterial carbon dioxide tension were unchanged, thereby normalizing for all variables except arterial oxygen tension. Lactate was not produced during maintained autoregulation either before or after PFC hemodilution.

In group B and C dogs, myocardial oxygen consumption (14.5±3.6 ml/min/100 g) was unchanged both between treatment groups and within groups at control coronary blood flow levels, at the LPL, and at 75% and 50% of control coronary blood flow levels throughout these experiments. Lactate was not produced throughout these experiments. Mean percent lactate extraction levels varied from 24% to 48% before and after PFC hemodilution. The only significant difference observed was for an increased percent lactate extraction (26.4±11.9 vs. 35.3±23.1, p<0.05) at the LPL in group C dogs with 100% oxygen supplemented with room air ventilation compared with room air ventilation alone.

**Pressure-Flow Relations**

Circumflex artery pressure-flow relations during maximal vasodilatation (group A) before and after PFC hemodilution for the total posterior LV myocardium (radiolabeled microspheres) are shown in Figure 1. Total blood flow in the LV posterior wall was correlated with mean circumflex coronary pressure. The pressure-flow relations for total blood flow and blood flow in the epicardial and endocardial layers were linear throughout the range of coronary perfusion pressures studied both before and after PFC hemodilution. The slopes of the calculated regression lines and the zero-flow intercepts on the pressure axis were unchanged for the total myocardium and for each of the myocardial layers.

Circumflex artery pressure-flow relations during maintained autoregulation (group B) before and after PFC hemodilution are illustrated in Figure 2. All of the pressure-flow relations were qualitatively similar. The effect of PFC hemodilution on mean circumflex artery blood flow and on total endocardial and epicardial blood flow at control (i.e., 100% mean blood flow, at the LPL, at 75%, and at 50% of control blood flow is shown in Table 2. Circumflex artery blood flow, measured with either the electromagnetic flow probe (ml/min) or with radiolabeled microspheres (ml/min/100 g) decreased from the control coronary perfusion pressure to the LPL before and after PFC hemodilution; after PFC hemodilution, circumflex artery blood flow increased, but these changes did not achieve a level of statistical significance. Because coronary blood flow did not change significantly during maintained autoregulation, we have set the higher coronary perfusion pressure at 80 mm Hg in all dogs for the purpose of comparison. Before PFC hemodilution, the mean LPL was 55±9 mm Hg, whereas after PFC hemodilution, it was 39±10 mm Hg (p<0.001). This leftward shift of the LPL with PFC hemodilution was observed in each dog (Table 2) with the electromagnetic flow probe (coronary blood flow) pressure-flow relation and was further confirmed with microsphere blood flow data (myocardial blood flow) and was a significant treatment effect (p<0.022). During PFC hemodilution with 100% oxygen supplemented with room air ventilation, mean coronary blood flow, total blood flow, and endocardial and epicardial blood flow were unchanged at the lower LPL.

When circumflex artery blood flow was lowered from 75% to 50% of control levels, coronary diastolic perfusion pressure decreased to 26±4 and 21±9 mm Hg before and after PFC hemodilution, respectively. At these lower levels of coronary blood flow.
perfusion pressure, endocardial blood flow increased significantly because of PFC hemodilution, whereas no change could be detected in the epicardial tissue layer. Myocardial lactate arterocoronary sinus difference remained positive for each dog. Total myocardial blood flow primarily reflects alterations in blood flow throughout the myocardial wall and thus only partly reflects changes in blood flow that occur predominantly in the endocardial tissue layer. A further confirmation of this data is indicated by the endocardial-epicardial blood flow ratio, which increased \( p<0.004 \) from 0.44 ± 0.09 before to 0.57 ± 0.19 after PFC hemodilution even though coronary perfusion pressure was lower.

Circumflex artery pressure-flow relations during maintained autoregulation were constructed after PFC hemodilution during room air and 100% oxygen supplemented with room air ventilation (group C). The LPL shifted leftward after PFC hemodilution in all dogs; there was no difference between the circumflex artery pressure-flow relations obtained during either room air or 100% oxygen supplemented with room air ventilation. Arterial oxygen content was approximately 2.5 ml/dl greater in PFC-treated dogs with 100% oxygen supplemented with room air ventilation because of the increased oxygen dissolved in the fluorocarbon phase. Myocardial oxygen transport, during either room air or 100% oxygen supplemented with room air ventilation after PFC hemodilution, for both the endocardial and epicardial tissue layers is shown in Table 3. In group C dogs, an LPL of 39 mm Hg was observed, which was similar to the LPL observed in group B dogs after PFC hemodilution. When coronary perfusion pressure was greater than 39 mm Hg, endocardial and epicardial oxygen transport remained within the normal physiological range, and no effect was observed when 100% oxygen supplemented with room air was compared with room air ventilation after PFC hemodilution. Below the LPL, both endocardial and epicardial oxygen transport increased \( p<0.03 \) during 100% oxygen supplemented with room air ventilation; however, the beneficial effect of PFC hemodilution on oxygen transport was greater \( p<0.009 \) in the endocardial tissue layer.

**Discussion**

The major finding of these studies was that PFC hemodilution preserved coronary blood flow distribution distal to a coronary stenosis by shifting the lower pressure limit of the autoregulatory pressure-flow curve to the left. Coronary blood flow and oxygen transport in the endocardial tissue layer of PFC-treated dogs was maintained despite significant reductions in coronary perfusion pressure.

**Effects of Perfluorocarbon Hemodilution**

Fluosol-DA 20% is a low viscosity, stable emulsion comprising two fluorocarbon compounds (perfluorodecalin and perfluorotripropylamine) with high oxygen solubility, a nonionic surface active agent (Pluronic F-68), balanced salts, and other emulsion stabilizers. Pluronic F-68 may be responsible for some of the beneficial effects that have been demonstrated during myocardial ischemia, 10,11,23–25 Plu-
TABLE 2. Effect of Perfluorocarbon Hemodilution With 100% Oxygen Ventilation at Different Levels of the Coronary Pressure Flow Relation During Autoregulation

<table>
<thead>
<tr>
<th></th>
<th>CDP</th>
<th>CBF</th>
<th>MBF</th>
<th>Endo</th>
<th>Epi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control O₂</td>
<td>PFC O₂</td>
<td>Control O₂</td>
<td>PFC O₂</td>
<td>Control O₂</td>
</tr>
<tr>
<td>Control</td>
<td>80 ± 0</td>
<td>80 ± 0</td>
<td>57 ± 10</td>
<td>66 ± 12</td>
<td>99 ± 32</td>
</tr>
<tr>
<td>LPL</td>
<td>55 ± 9</td>
<td>39 ± 10</td>
<td>54 ± 7</td>
<td>58 ± 12</td>
<td>92 ± 33</td>
</tr>
</tbody>
</table>

Data are expressed as group mean ± SD.

CDP, coronary diastolic pressure (mm Hg); CBF, mean coronary blood flow (ml/min) measured with flow probe; MBF, Endo, Epi, total, endocardial, and epicardial blood flow (ml/min/100 g) measured with radiolabeled microspheres. Control O₂, no perfluorocarbon hemodilution (PFC) with 100% O₂ ventilation; PFC O₂, PFC hemodilution with 100% O₂ ventilation; Control, maintained autoregulation; LPL, lower pressure limit of autoregulatory pressure-flow relation; 75% and 50% of control blood flow.

Inter-group statistical comparison by two-way ANOVA with replication.22

Pneumonic F-68 reduces vascular resistance, lowers blood viscosity, and also reduces blood surface tension26,27; however, recent findings in patients have shown that Pluronic F-68 activates the complement cascade28 and is associated with an accumulation of white blood cells in the lungs. Although we did not specifically evaluate the effect of Pluronic F-68 on myocardial blood flow distribution, a group of dogs who received PFC but who were ventilated with room air was included in the present study. The emulsifier effect of PFC could therefore be compared in the absence and presence of oxygen-carrying capacity.

In the clinical setting, use of PFC is limited; several investigators have reported various adverse effects after PFC treatment, including transient hypotension,29 pulmonary insufficiency, reduced white cell count, reticuloendothelial system blockade, and transient complement activation.14,28-30 However, several recent reports describe the beneficial effects of PFC hemodilution during myocardial ischemia followed by reperfusion in dogs,3,31 as a volume expander in a canine model of hypoxemic respiratory failure,32 and during coronary angioplasty.7

During this study, eight dogs developed complications despite corticoid premedication. These complications, which occurred at the beginning of the experiment, were acute congestive heart failure in four dogs and severe hypotension with normal LV end-diastolic pressure in four dogs. However, the 16 other dogs did not develop hemodynamic anomalies and remained stable throughout the experiment.

Effect of Perfluorocarbon Hemodilution on Myocardial Blood Flow Distribution

To verify whether PFC hemodilution modifies coronary conductance and the zero-flow pressure, circumflex artery pressure-flow relations were constructed during adenosine-induced maximal vasodilation before and after PFC hemodilution (group A). During maximal vasodilation, coronary pressure-flow relations can be altered by changes in viscosity,4 by changes in zero-flow pressure,39 or by LV hypertrophy.34 In the present study, vascular conductance and zero-flow pressure were not changed throughout the myocardium despite the reduced hematocrit level (see Figure 2A), the increased heart rate, lower LV blood pressures, and the nonsignificant reduction of LV end-diastolic pressure. These results rule out significant changes in viscosity or edema after PFC hemodilution and are similar to the observations reported by O'Benar and Bellamy.33 Biro36 also reported a significant reduction in the hematocrit level after PFC hemodilution in dogs, but only a marginal change in vascular conductance was observed.

With maintained autoregulation, the LPL can be shifted upward and to the right during tachycardia,6 increased myocardial oxygen demand,2 and downward and to the right with increased blood viscosity.5 In the present study, the LPL of the coronary pressure-flow relation before PFC hemodilution was achieved at 55 ± 9 mm Hg. After PFC hemodilution, myocardial oxygen consumption was unchanged, but the LPL shifted leftward at 39 ± 10 mm Hg. In each dog, the LPL was determined before injection of microspheres and again at the time of microsphere injection; the LPL indicated a similar leftward shift. Furthermore, at the LPL, a good correlation for blood flow measurements was obtained with two independent blood flow measurement techniques (Table 2). Total blood flow to the circumflex artery perfusion bed was maintained despite the lower coronary perfusion pressure. This was primarily due to the ability of the endocardial vessels to maintain autoregulation at the lower coronary perfusion pressure of 39 ± 10 mm Hg because myocardial oxygen consumption was unchanged; there-
TABLE 3. Effect of Perfluorocarbon Hemodilution With Room Air or 100% Oxygen Ventilation and of Coronary Pressure on Oxygen Transport

<table>
<thead>
<tr>
<th>Diastolic circumflex pressure treatment</th>
<th>≤39 (mm Hg)</th>
<th>≥40 (mm Hg)</th>
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<tbody>
<tr>
<td>PFC RA</td>
<td>PFC O₂</td>
<td>PFC RA</td>
</tr>
<tr>
<td>Epi O₂ Transport (ml/min/100g)</td>
<td>6.6±4.0</td>
<td>11.4±7.0</td>
</tr>
<tr>
<td>p (PFC RA vs. PFC O₂)</td>
<td>0.027</td>
<td>NS</td>
</tr>
<tr>
<td>p (Epi vs. epi)</td>
<td>0.009</td>
<td>NS</td>
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<tr>
<td>p Interaction</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>df: 1,16</td>
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</tbody>
</table>

Values are mean ± SD.

The range of diastolic circumflex pressure in the ≤39 mm Hg group was 18–39 and 20–39 mm Hg in the PFC RA and PFC O₂ treatment groups, respectively. In the ≥40 mm Hg group, the range of diastolic circumflex pressure was 40–110 and 40–108 mm Hg in the PFC RA and PFC O₂ treatment groups, respectively.

PFC RA, perfluorocarbon hemodilution with room air ventilation; PFC O₂, PFC hemodilution with 100% O₂ ventilation; Epi and Epi O₂ Transport, endocardial and epicardial oxygen transport (ml/min/100 g); NS, not significant.

Intergroup statistical comparisons (n = 20) for each coronary pressure group by two-way ANOVA with replication.

After, blood flow was pressure dependent (p<0.002). The epicardial vessel capacity to autoregulate was substantially greater than the endocardial vessels and was not lost for the range of coronary perfusion pressures studied either before or after PFC hemodilution. Based on data from group A, a significant viscosity effect was ruled out because circumflex artery pressure-flow relations were not changed.

Among the factors that control steady-state coronary pressure-flow relations, changes in back pressure rather than PFC hemodilution may have been responsible for the leftward shift of the LPL. However, in the present study, zero-flow pressure was unchanged during PFC hemodilution and LV enddiastolic, and coronary sinus pressures were always lower than zero-flow pressure throughout these experiments. Myocardial ischemia, which could also produce a similar coronary pressure-flow relation at low coronary perfusion pressure, was ruled out because after PFC hemodilution none of the dogs produced lactate even at 50% of control blood flow levels. Prevention of ischemia with oxygenated Fluosol-DA has been shown by Cleman et al² during coronary angioplasty and also by Tokioka et al³ who showed preservation of myocardial function and metabolism during brief coronary occlusions.

An intrinsic component of the coronary vessel, which is responsive to arterial oxygen concentration, may also be responsible for the adjustment of vascular tone and consequently the alteration in flow during PFC hemodilution. The beneficial effect of PFC hemodilution may occur as a consequence of increased diffusion of oxygen from fluorocarbons into the tissue, which is perhaps due to the small particle size of the fluorocarbon emulsion, or as a consequence of reduced affinity of the blood and PFC mixture for oxygen even in the absence of increased oxygen content or blood flow. PFC hemodilution without 100% oxygen supplemented with room air ventilation also produced a leftward shift of the LPL in the present study. However, with 100% oxygen supplemented with room air ventilation, endocardial oxygen transport was significantly increased compared with PFC hemodilution with room air ventilation alone. This suggests that it is not only the oxygen-carrying capacity of the fluorocarbon emulsion that is responsible for its beneficial effects. The results of this study support the hypothesis that the reduction of ischemic injury by PFC may be partly due to a mechanism other than direct enhancement of oxygen delivery²⁵ because fluorocarbon emulsions, even during room air ventilation, may increase washout of protons and metabolic by-products of ischemia or may recruit capillary beds at the lower coronary perfusion pressures. An important question that has not been resolved in this study is whether PFC hemodilution shifts the LV pressure-volume relation. Such a shift may have contributed to the treatment effect by reducing myocardial oxygen demand; however, myocardial oxygen consumption remained constant throughout these studies.

Conclusions

Our data are the first to demonstrate that an intervention such as PFC hemodilution can preserve myocardial blood flow distal to a coronary stenosis. This is achieved both by a leftward shift of the LPL and by an increased oxygen-carrying capacity. The ability of PFC emulsions to transport oxygen is of potential clinical importance in patients with coronary artery disease because it may improve the efficacy of the coronary angioplasty technique by permitting increased durations of balloon inflation. Thus, the development of PFC emulsions that are better tolerated than Fluosol-DA 20%, but which have similar coronary dynamic properties, may be important for improving transmural blood flow distribution and oxygen transport economy.
Acknowledgments

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References


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