Perflubron Emulsion Does Not Cause Neutrophil (PMN) Activation In-Vivo.

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ABSTRACT

 Earlier, we reported that in-vitro incubation of blood for ten minutes with the perfluorocarbon (PFC) emulsion Fluosol increased leukocyte activation as determined by adhesion to nylon fiber. In this study, we examined if in-vivo treatment with these PFC emulsions affected the expression of the leukocyte adhesion protein CD11b (primarily found on PMNs) and the generation of leukocyte-derived reactive oxygen species (ROS, oxygen free radicals). Rats were anesthetized and catheterized. Three groups were studied: 1) a phosphate buffered saline (PBS) control group (n=6), 2) a group treated with Fluosol emulsion (1.08g PFC/kg, n=6) and 3) a group treated with perflubron emulsion (1.08g PFC/kg, n=6). Blood samples were taken before and 10, 20, 40 and 60 minutes after treatment for hematology and analysis of PMN CD11b expression and ROS production using flow cytometry. We found that Fluosol caused significant increases in both neutrophil surface expression of CD11b and ROS generation (p<0.05, ANOVA). In the Fluosol group, the peak responses in PMN CD11b expression and ROS production were observed ten minutes after treatment. In contrast, treatment with perflubron emulsion did not cause a significant increase in CD11b expression nor an increase in ROS production at any time after treatment. These findings suggest that Fluosol causes a transient PMN activation in-vivo. The activation of circulating PMNs, in-vivo, is sufficient to significantly enhance oxygen derived free radical production. The lack of a PMN response to perflubron emulsion in-vivo suggests that this agent is not likely to induce a leukocyte-mediated inflammatory response.

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INTRODUCTION

Due to their oxygen solubility properties, perfluorocarbon emulsions were developed for use as oxygen carrying solutions to serve as temporary blood substitutes (1,2). Perfluorocarbons (PFCs) are compounds with cyclic or straight chain carbon backbones and have complete replacement of hydrogen with fluorine. Perfluorocarbons are insoluble in blood and require an emulsification process to increase solubility. Perfluorocarbon emulsions may be useful in the settings of cardiac surgery and extracorporeal circulation for several reasons. One PFC emulsion, Fluosol-DA, has been reported to have cardioprotective properties, limiting myocardial ischemia-reperfusion injury (3,4,5,6). The beneficial effect appears to be independent of Fluosol’s oxygen carrying capacity, low viscosity and small particle size (0.1-0.3 um) (7,8). A mechanism proposed to explain the cardioprotective effects of Fluosol is modulation of leukocyte activation, limiting the leukocyte contribution to ischemia-reperfusion injury (3,9,10). Some studies indicate that Fluosol provides cardioprotection by inhibiting neutrophil function (7), including neutrophil chemotaxis, phagocytosis and superoxide radical production (1,12). This agent may also interfere with neutrophil expression of adhesion molecules limiting adherence to endothelial cells and decreasing the neutrophil’s involvement in the acute inflammatory response during reperfusion (11).

In follow-up studies, it was later learned that, rather than inhibit neutrophil activation, Fluosol activates neutrophils (10,13). A different hypothesis was then proposed to explain the observed cardioprotective effects of Fluosol during cardiac surgery and extracorporeal circulation. That is, Fluosol may possibly protect the cardiac tissue by causing a release of damaging oxygen free radicals and proteases from the circulating neutrophils, while the heart is crossclamped. The neutrophils would then be in a “refractory” state when the aortic crossclamp is released and the heart is reperfused, limiting the neutrophil contribution to reperfusion injury (9,13). Another hypothesis proposed to explain how activating neutrophils could be cardioprotective is that Fluosol-induced activation may cause neutrophils to marginate in other vascular beds, thereby “distracting” the neutrophils from participating in myocardial reperfusion injury following crossclamp release (13). It is possible that the cardioprotective effects of Fluosol are via modulating neutrophil function, but the exact mechanism(s) by which Fluosol provides cardiac protection from myocardial ischemia-reperfusion injury remains unclear.

The initial step in the neutrophil contribution to myocardial ischemia-reperfusion injury is leukocyte deposition in the microcirculation of the heart (14,15). Following neutrophil activation there is an increase in adhesion molecule expression and neutrophil adherence. The neutrophil’s surface membrane expresses a glycoprotein (CD11b) associated with neutrophil adhesion. In the presence of a chemotactic stimulator, such as formyl-methionyl-leucyl-phenylalanine (fMLP), CD11b expression is upregulated (16). Previous reports have confirmed two to ten fold increases of CD11b over resting values following neutrophil stimulation (17,18). Neutrophils also respond to stimulation by generating an oxidative burst, whereby reactive oxygen species (ROS) are produced. Release of significant ROS by the neutrophil can cause oxygen radical-mediated injury to the tissues (19).

The purpose of this study was to compare the effects of two perfluorocarbon emulsions, on leukocyte function and activation in-vivo. We compared the white blood cell response to a first generation agent, Fluosol-DA and a second generation agent, perflubron emulsion. In a previous study, we compared the effects of Fluosol and perflubron emulsion on leukocyte adhesion in-vitro, finding that Fluosol had a direct stimulatory effect on leukocyte function (20). Fluosol increased leukocyte adhesion while perflubron emulsion had no effect on granulocyte adhesion compared to a phosphate buffered saline (PBS) control. The effects of PFC emulsions on neutrophil function and activation in-vivo are less clear. As mentioned, earlier studies found that in-vivo administration of Fluosol either suppressed neutrophil function (3,12) or activated neutrophils (10,21,22). Fewer studies have been performed to determine the effects of second generation PFC emulsions on neutrophil function in-vivo. In this study, we found that intravascular administration of Fluosol caused a transient neutrophil activation, as demonstrated by significant increases in both the expression of the neutrophil adhesion protein CD11b and the production of oxygen free radicals. Administration of perflubron emulsion, on the other hand, did not cause neutrophil activation.

MATERIALS AND METHODS

Experimental Protocol. All animal experiments in this study were performed in accordance with the Guide for the Care and Use of Laboratory Animals (23). Adult Sprague-Dawley rats (400-600g), were anesthetized with sodium pentobarbital (50mg/kg, IP). The animals were placed in a supine position on a Deltaphase Isothermal Pad®. The femoral artery was cannulated and connected to a blood pressure transducer® for measuring arterial blood pressure and heart rate. The rectal temperature was monitored with a telethermometer and body temperature was maintained with the isothermal pad.

Baseline, control measurements of heart rate, blood pressure and body temperature were collected and a one milliliter blood sample was taken for arterial blood gas analysis, hematology and flow cytometry. Then phosphate buffer saline (PBS, 5.4ml/kg, n=6), or Fluosol (1.08g/kg, n=6), or perflubron emulsion (1.08g/kg, n=6) was infused through the arterial cannula. Fluosol and perflubron emulsions have different perfluorocarbon
concentrations (20% vs. 60% w/v, respectively), thus the emulsion doses were adjusted to deliver the same PFC dose of 1.08g PFC/kg. Following treatment, arterial blood pressure, heart rate and body temperature were measured continuously for one hour. At 10, 20, 40 and 60 minutes after agent administration, blood samples were taken for blood gas analysis, hematology, and flow cytometry. Following the 60 min measurements, 7 ml of blood were withdrawn into a heparinized syringe for the in-vitro leukocyte adhesion assay.

Blood Gases and Hematology. Arterial blood gases (pH, pCO₂, PO₂) were measured in a blood gas analyzer. Blood cell counts (total white cells, red blood cells, platelets, hematocrit) were made using an automated hematology analyzer.

Expression of CD11b and ROS Production. DCFH-DA (2',7'-dichlorofluorescin diacetate) is a fluorescent probe used to quantify intracellular ROS production. DCFH-DA diffuses into the neutrophil’s cytoplasm where it is enzymatically deacetylated to nonfluorescent 2',7'-dichlorofluorescin (DCF), trapping it within the cell. In the presence of ROS, DCFH is oxidized to the fluorescent compound dichlorofluorescein (DCF). DCF fluorescence can be quantified using flow cytometry analysis (24,25). At each time point, blood samples were collected for analysis of the neutrophil’s CD11b adhesion molecule surface expression (26) and the ROS production. Blood samples were first incubated with LDS-751 (1.0 ug/ml), a fluorescent nuclear stain, at 37°C for 10 minutes. LDS-751 staining allows the separation of fluorescent leukocytes (nucleated) from non-fluorescent erythrocytes (non-nucleated) when using flow cytometry (27). The whole blood and LDS mixture samples were divided into five 250 ul aliquots for flow cytometry analysis: 1) PBS, 2) anti-CD11b/FITC mAb (5.0 ug/ml), 3) anti-CD11b/FITC mAb and fMLP (10-7M), 4) DCFH-DA (80uM) or 5) DCFH-DA and fMLP.

Blood samples treated with anti-CD11b mAb or DCFH-DA were incubated for 15 minutes at 37°C, followed by incubation with either fMLP (10-7M) or PBS for 10 minutes at 37°C. The samples were then diluted with 4 ml PBS (4°C) and placed on ice until analysis. Measurement of anti-CD11b/FITC and DCF fluorescence was performed using flow cytometry. Neutrophils and lymphocytes were identified on the basis of their size (forward scatter) and granularity (side scatter). Back-gating was used to focus on the sub-population of granulocytes (26). The neutrophils CD11b surface expression and ROS production were expressed as the total fluorescence intensity (TFI) which was the product of mean channel fluorescence and percent positive events of the fluorescent probes.

Leukocyte Adhesion Assay. The leukocyte adhesion assay was described by us previously (20,28). Briefly, 40 mg of scrubbed nylon fiber was packed to the 0.2 ml mark of 1 ml tuberculin syringe barrels. A 25 gauge needle was attached to the syringe barrel and the barrels were suspended over 2 ml collecting tubes. In a 37°C warm room, 0.9 ml of blood was pipetted onto each column and the effluents were collected for ten minutes. Blood cell counts (total white cells, red blood cells, platelets) were performed of the blood that was applied to the columns, as well as the blood effluent from the columns. Manual differential blood cell counts were made for all blood samples. The percent WBC adherence is calculated as: 1-(WBC_column/WBC_pre), where pre is the blood sample applied to the column and post is the effluent from the column. For each animal, at least three columns were run for each blood-PFC mixture evaluated.

e Model ABL-330, Radiometer, LaVerne, CA
f Model 9018, Serono Diagnostics, Allentown, PA
g FACScan Flow Cytometer, Becton Dickenson, San Jose, CA

Table 1: Heart rate, MAP, and arterial blood gases for the PBS, Fluosol and perflubron treated groups

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th></th>
<th>POST 20min</th>
<th></th>
<th>POST 60min</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBS</td>
<td>Fluosol</td>
<td>Perflubron</td>
<td>PBS</td>
<td>Fluosol</td>
<td>Perflubron</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>347±10</td>
<td>317±22</td>
<td>358±13</td>
<td>318±12</td>
<td>355±22</td>
<td>295±5</td>
</tr>
<tr>
<td>MAP</td>
<td>127±4</td>
<td>132±8</td>
<td>140±4</td>
<td>101±11</td>
<td>109±10</td>
<td>94±5</td>
</tr>
<tr>
<td>pH</td>
<td>7.34±0.01</td>
<td>7.31±0.01</td>
<td>7.36±0.02</td>
<td>7.37±0.01</td>
<td>7.33±0.02</td>
<td>7.37±0.01</td>
</tr>
<tr>
<td>PCO₂</td>
<td>46.6±2.3</td>
<td>48.9±2.1</td>
<td>44.3±2.1</td>
<td>44.6±1.8</td>
<td>48.4±3.6</td>
<td>42.2±1.0</td>
</tr>
<tr>
<td>PO₂</td>
<td>71.7±4.1</td>
<td>61.4±4.7</td>
<td>74.5±2.2</td>
<td>71.1±2.7</td>
<td>68.9±4.8</td>
<td>73.0±2.3</td>
</tr>
</tbody>
</table>

*Fluosol significantly different from the perflubron group (P<0.05)
Table 2: Leukocyte, granulocyte, and lymphocyte counts as a percent of the pre-treatment control for the PBS-control, Fluosol, and perflubron treated groups 20, 40, and 60 minutes after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Leukocyte Count</th>
<th>Granulocyte Count</th>
<th>Lymphocyte Count</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20min</td>
<td>40min</td>
<td>60min</td>
</tr>
<tr>
<td>PBS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluosol</td>
<td>123.6±6.1*</td>
<td>108.2±12.3</td>
<td>100.9±11.1</td>
</tr>
<tr>
<td>Perflubron</td>
<td>98.6±5.4</td>
<td>93.1±4.5</td>
<td>108.4±5.0</td>
</tr>
</tbody>
</table>

*Fluosol significantly different from the perflubron and PBS groups (P<0.05)

**Data Analysis.** Data was collected and tabulated on computer spreadsheets. Statistical analyses were performed using a computer program. The summary group data were expressed as mean ± SE. Differences among groups were assessed with an ANOVA. Post hoc testing was performed when the results of the ANOVA were significant. Differences were considered statistically significant at the p<0.05 level.

**RESULTS**

Table 1 summarizes the results of the measurements of heart rate, mean arterial blood pressure (MAP), and arterial blood gases for the PBS-control, Fluosol and perflubron treated groups prior to and 20 and 60 minutes after treatment. There were no differences in the heart rate, MAP, or blood gases between the three treatment groups before drug administration. Body temperature was maintained at 37°C (range 36.0 - 37.5°C) for all three groups during all time points in the study. The PBS, Fluosol and perflubron groups had no statistically significant changes in MAP, or blood gases during the 60 minutes following treatment. All groups demonstrated a decrease in MAP with time, perhaps due to the anesthetic, but there were no statistically significant differences in MAP among the three groups. The Fluosol group had a significantly higher heart rate then the perflubron group 20 minutes after treatment (p<0.05). There was no difference in the heart rate among the three groups 60 minutes following treatment.

Table 2 gives the circulating leukocyte counts for the PBS, Fluosol and perflubron groups, expressed as the percent of pre-treatment control. Prior to treatment, all blood cell counts, leukocytes, platelets and red cells, were quite similar for all groups. Following treatment, the platelet counts and hematocrits were not different among the groups. However, there was a significant increase in the leukocyte count in the Fluosol group by 20 minutes (p<0.05). By 40 and 60 minutes, the leukocyte, granu-
Figure 2: The flow cytometry analysis of the PMN's CD11b surface expression for the PBS, Fluosol, and perflubron groups before and 10, 20, 40, and 60 minutes after treatment.

**DISCUSSION**

Fluosol-DA, a first generation PFC emulsion, consists of two perfluorocarbons, perfluorodecalin and perfluorotripropylamine in a 20% weight per volume emulsion consisting of a detergent, Pluronic F-68, and a surfactant, egg-yolk phospholipids (29). Perflubron emulsion, a second generation PFC emulsion, consists almost entirely of a single perfluorocarbon, perfluorooctylbromide, in an emulsion consisting of egg-yolk phospholipids (30). Currently perflubron is being tested in Phase II clinical studies for use in conjunction with hemodilution during elective surgery or cardiopulmonary bypass procedures (31). Early studies with Fluosol...
suggested that this PFC emulsion inhibited leukocyte function (3, 11, 32). However, later studies found that incubation of blood with Fluosol stimulated PMNs (10, 13, 20). In the current in vivo study, we found that Fluosol caused a PMN activation as demonstrated by both a significant increase in CD11b adhesion molecule expression and ROS production by the phagocytic PMNs.

The PMN response to Fluosol appeared to vary with time following treatment (Figures 2, 3). For PMN CD11b, the expression was significantly increased throughout the 60 minute observation period. However, PMN ROS production was significantly increased only 10-20 minutes after treatment. The transient nature of the PMN response to Fluosol treatment may be explained in two ways. First, the CD11b adhesion molecules expressed on the surface of the PMNs may be shed or returned to internal cellular compartments. However, this possibility is unlikely because other studies suggest that expressed CD11b is not shed rapidly. For example, Miller et al (33) found a rapid increase in the PMN CD11b expression ten minutes following fMLP [10^-7 M] stimulation. There was a further increase in the PMN CD11b expression by 60 minutes following stimulation with no indication of a decline of expression (33). Thus, in the one hour observation period of our study, it is unlikely that CD11b adhesion molecules were significantly shed or re-internalized, causing CD11b expression to decrease.

A second possibility is that the neutrophils sampled later during the observation period are from a different cell population than those initially sampled. The increased PMN CD11b adhesion protein expression following Fluosol treatment may have caused PMN adherence to the vasculature. Thus, the activated blood cells will effectively leave the circulating pool of PMNs. Then the blood sampled later in the experiment contained those PMNs that did not adhere in response to the earlier stimulation. The notion of changes in the circulating pool of PMNs following stimulation is not novel. Appen et al measured the effects of hemodialysis membrane materials on leukocyte activation (34). Following exposure of blood to the membrane surfaces, neutrophil CD11b expression was increased within the first three minutes, but returned to pre-exposure levels after 60 minutes. Appen et al concluded that the neutrophils sampled three minutes after exposure were not the same cells sampled at 15 and 60 minutes after exposure. The activated neutrophils (increased CD11b expression) could adhere to the vascular endothelium, causing the measured CD11b fluorescence of the residual circulating population of cells to be lower.

In contrast to the sustained increase in CD11b expression and transient increase in ROS production with Fluosol, treatment with perflubron emulsion did not stimulate the PMNs. Other studies also report no increase in PMN activity with perflubron. In fact, at higher concentrations, perflubron may decrease PMN activity. In a recent in-vitro study, Rossman et al (35) reported that human neutrophils treated with perflubron produced significantly less ROS and had a significantly decreased chemotactic response to PMA stimulation. In another study, Smith et al (36) reported a decrease in ROS production by alveolar macrophages after in-vitro exposure to perflubron emulsion. Previously, we

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### Table 3: PMN CD11b expression and ROS production in unstimulated and fMLP-stimulated blood samples for the PBS, Fluosol, and perflubron treated groups

**CD11b Expression**

<table>
<thead>
<tr>
<th>Time</th>
<th>PBS Unstimulated</th>
<th>PBS Stimulated</th>
<th>Fluosol Unstimulated</th>
<th>Fluosol Stimulated</th>
<th>Perflubron Unstimulated</th>
<th>Perflubron Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE</td>
<td>175.9±19.5</td>
<td>696.8±47.9</td>
<td>178.2±20.8</td>
<td>727.6±70.0</td>
<td>171.4±13.1</td>
<td>631.0±59.2</td>
</tr>
<tr>
<td>10min</td>
<td>226.2±27.2</td>
<td>724.0±42.4</td>
<td>436.5±53.3</td>
<td>975.1±55.5</td>
<td>223.3±9.6</td>
<td>695.4±32.2</td>
</tr>
<tr>
<td>20min</td>
<td>187.9±27.2</td>
<td>767.5±53.4</td>
<td>333.8±11.6</td>
<td>850.2±72.9</td>
<td>179.2±25.9</td>
<td>735.2±54.6</td>
</tr>
<tr>
<td>40min</td>
<td>187.1±31.9</td>
<td>783.0±47.9</td>
<td>274.6±21.2</td>
<td>760.1±45.3</td>
<td>163.9±20.1</td>
<td>699.6±65.6</td>
</tr>
<tr>
<td>60min</td>
<td>170.6±29.5</td>
<td>641.7±171</td>
<td>250.0±24.9</td>
<td>902.4±60.0</td>
<td>151.3±14.5</td>
<td>723.9±50.3</td>
</tr>
</tbody>
</table>

**ROS production**

<table>
<thead>
<tr>
<th>Time</th>
<th>PBS Unstimulated</th>
<th>PBS Stimulated</th>
<th>Fluosol Unstimulated</th>
<th>Fluosol Stimulated</th>
<th>Perflubron Unstimulated</th>
<th>Perflubron Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE</td>
<td>58.1±13.4</td>
<td>164.9±20.3</td>
<td>66.7±15.2</td>
<td>163.3±24.1</td>
<td>73.8±20.5</td>
<td>147.9±19.2</td>
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<tr>
<td>10min</td>
<td>46.7±20.0</td>
<td>180.6±48.1</td>
<td>118.6±7.6</td>
<td>343.8±27.1</td>
<td>39.1±4.4</td>
<td>173.2±18.7</td>
</tr>
<tr>
<td>20min</td>
<td>53.3±11.2</td>
<td>178.1±14.2</td>
<td>94.6±13.4</td>
<td>283.7±49.0</td>
<td>46.7±6.8</td>
<td>163.4±6.4</td>
</tr>
<tr>
<td>40min</td>
<td>71.4±20.0</td>
<td>197.8±28.7</td>
<td>85.4±14.9</td>
<td>274.6±58.6</td>
<td>55.2±4.4</td>
<td>217.0±11.6</td>
</tr>
<tr>
<td>60min</td>
<td>50.3±11.6</td>
<td>178.0±38.0</td>
<td>53.9±12.3</td>
<td>230.7±48.9</td>
<td>48.3±9.2</td>
<td>218.2±30.8</td>
</tr>
</tbody>
</table>
compared the effects of Fluosol and perflubron emulsion on leukocyte adhesion in vitro, finding that Fluosol had a direct effect on leukocyte function (20). In a separate, in-vivo study, we found that treatment with perflubron emulsion significantly decreased neutrophil adhesion (37). The lack of a perflubron effect on neutrophil adhesion in the current study versus a significant decrease in PMN adhesion in our earlier in-vivo study may be due to the dose of perflubron emulsion administered. In the earlier in-vivo study, the dose of perflubron emulsion was two and a half times more than the dose used in the current study. Thus, the ability of perflubron emulsion to limit leukocyte stimulation may be a function of dose. The dose of perflubron emulsion used in the current study is the same dose currently being evaluated in clinical trials.

All three groups demonstrated a decrease in MAP with time. This decrease may be related to the deep plane of pentobarbital anesthesia, but all MAPs were within normal limits for anesthetized animals.

There was a significant increase in the number of circulating leukocytes in the Fluosol treated group at 20 minutes following treatment. Fluosol treatment may have caused a net demargination of leukocytes increasing the number of circulating leukocytes. Neither of the perfluorocarbon treatments had any effect on hematocrit or platelet count.

Previous studies suggested that activation of neutrophils by Fluosol may cause the cells to be refractory to further stimulation (9,13). This hypothesis is not supported by our findings. As indicated in Table 3, before and at all times after emulsion treatment, all groups were quite responsive to tMLP stimulation, as indicated by significant increases in both CD11b expression and ROS production (~200-400% of unstimulated samples). At no time during the one hour observation period did either emulsion limit the PMNs from responding to the chemotactic peptide fMLP. Perhaps another mechanism, such as "distracting" the activated leukocytes to non-coronary vasculatures, is the way in which Fluosol exerts cardioprotection.

In contrast to our earlier report, in the current study, at t=60min, we did not observe a difference in granulocyte adhesion for the Fluosol and perflubron emulsion groups. The different findings between our in-vitro and in-vivo studies may be explained by differences in the experimental protocols. That is, both the PFC doses and the incubation periods were different in the two studies. The dose of PFC emulsions incubated with the blood in this in-vivo study was less than the dose used in the previous in-vitro study. Also, in the previous study, blood was incubated in-vitro with the PFCs for 10 minutes before being tested in the nylon fiber adhesion columns. In this study, blood was tested 60 minutes after treatment. Perhaps the lower dose of emulsion was not sufficient to effect granulocyte adhesion, or by 60 minutes after treatment those leukocytes in the circulating blood pool were less active. The results from the nylon column adhesion assay support the flow cytometry results for PMN ROS that, 60 minutes after treatment, those PMNs in the circulating blood pool were not significantly activated.

There have been previous reports that cardiopulmonary bypass (CPB) stimulates a leukocyte-mediated inflammatory response (38,39). PFCs are currently being investigated for use in conjunction with hemodilution during CPB procedures (31,40). Previous studies using animal models of CPB suggest that PFC emulsions are effective oxygen carrying solutions and may serve as excellent prime solutions during cardiac surgery (41,42). The effects of PFC emulsions on leukocyte activation are not yet fully understood. An added benefit of some PFC emulsions may be to help limit the inflammatory response during and after CPB. Future studies are required to determine if addition of PFC emulsions to the CPB circuit will effect the inflammatory response.

In conclusion, these findings indicate that both in-vivo and in-vitro blood treatment with Fluosol causes leukocyte activation, as demonstrated by an increase in CD11b adhesion molecule expression and ROS production. The lack of a PMN response to the clinical dose of perflubron emulsion, in-vivo, suggests that this agent is not likely to induce a leukocyte-mediated inflammatory response. Perflubron is an oxygen carrying agent that might be well suited as a priming solution for the CPB circuit.

REFERENCES


37. Wilson DS, McDonagh PF. Granulocyte adherence is reduced by in-vivo incubation with the perfluorocarbon blood substitute, perflubron emulsion. J Leuk Biol Supplement. 1994; 27.


