Clinical Investigations in Critical Care

Effect of Fast vs Slow Intralipid Infusion on Gas Exchange, Pulmonary Hemodynamics, and Prostaglandin Metabolism*

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Intralipid (20 percent, 500 ml) was infused fast (5 h) or slow (10 h) randomly in patients with lung injury to relate changes in plasma prostaglandin (PG) concentrations to gas exchange and pulmonary hemodynamics. Data were collected at baseline, midpoint of infusion, and 2 h following infusion. Vasodilator and vasoconstrictor PG metabolites, 6-keto-PGF1α, and thromboxane B2, respectively, were measured in radial arterial blood samples. Slow Intralipid infusion increased shunt fraction (Qs/Qt) without changing mean pulmonary artery pressure (MPAP), whereas fast Intralipid infusion increased MPAP without changing Qs/Qt. Prostaglandin levels did not change significantly during either infusion. However, in both groups when the PG substrate was removed, hemodynamic and metabolite values decreased in parallel. In conclusion, we were unable to demonstrate a cause and effect relationship between plasma levels of 6-keto-PGF1α and thromboxane B2 and the observed pulmonary hemodynamic response to slow or fast Intralipid infusion. (Chest 1991; 99:426-29)

Commerially available isotonic fat emulsions (Intralipid and Liposyn) are commonly used in critically ill patients as a caloric source and to prevent essential fatty acid deficiency. Both experimental and clinical studies have documented gas exchange disturbances following intravenous fat emulsion (IVFE) infusion.†‡ Postulated mechanisms for this alteration in gas exchange include triglyceride-associated decreases in diffusion capacity and fatty acid–induced lung injury.§ A more recent study, however, has attributed the gas exchange abnormalities to increased plasma levels of prostaglandins (PG) during IVFE administration.¶ The PG may cause gas exchange disturbances by altering pulmonary vasomotor tone and consequently ventilation-perfusion relationships. Skeie et al⁵ have suggested that the quantity and the type of PG produced is dependent on the rate and duration of infusion. The magnitude of IVFE-related impairment of gas exchange may be greater in the presence of preexisting acute lung injury. The present study was designed to document the magnitude of Intralipid–related alterations in gas exchange in patients with acute lung injury and to determine whether any such alterations can be attributed to the Intralipid acting as a substrate for increased PG production.

Materials and Methods

Fifteen multiple trauma patients with adult respiratory distress syndrome (ARDS) and sepsis were included in the study. ARDS was defined by the following criteria: (1) clinical diagnosis: chest roentgenogram showing unilateral or bilateral pulmonary infiltrates with normal cardiac silhouette; (2) refractory hypoxemia by laboratory criteria with patients requiring FiO2 ≥0.5, PEEP 10 cm or greater, and PaO2/FiO2 ratio <250; (3) normal cardiac function as demonstrated by pulmonary capillary wedge pressure <18 mm Hg; and (4) lung injury score ≥2.5.†

Sepsis was defined as a positive blood culture or operative evidence of infection or abscess or chest roentgenogram compatible with pneumonia with positive laboratory findings. Laboratory criteria include the following: (1) temperature ≥38.5°C; (2) WBC count ≥15,000 or <5,000/cu mm; and (3) hyperdynamic hemodynamic status.

Informed consent was obtained from each patient or guardian prior to enrolling them in the study. All patients had an indwelling arterial catheter and a thermistor-tipped Swan-Ganz catheter because of the severity of their illness. At the time of the study,
patients were not receiving vasoactive or anti-inflammatory drugs. Baseline data measurements included the following: arterial and mixed venous blood gas tensions, right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), PA diastolic pressure (PAD), pulmonary capillary wedge pressure (PCWP), and cardiac output. Hemodynamic indices and Qs/Qr were calculated using standard formulas.

When the patients met the study criteria for ARDS and sepsis, they were randomized to either a standard slow infusion (10 h) or a fast infusion (5 h) by selecting a sealed envelope containing standard slow or fast infusion instruction.

Stable metabolites of the vasodilator (PGF₁α) and vasoconstrictor (thromboxane A₂) PGs, i.e., 6-keto-PGF₁α and thromboxane B₂, respectively, were measured as indicators of endogenous PG synthesis. For plasma PG measurement, 10-ml samples of radial arterial blood were drawn during baseline, midpoint, and at 2 h after infusion. Blood specimens were drawn at the same time the hemodynamics and gas exchange data were obtained. Samples were collected in syringes containing 40 mg of EDTA as an anticoagulant and 10 mg of indomethacin as a PG synthetase inhibitor. Samples were spun immediately at 3,200g for 10 minutes at 4°C. Plasma was collected and stored at −70°C until assayed. For PG extraction, plasma samples were acidified to a pH of 3.0 with citric acid and centrifuged to remove precipitated protein. Samples passed through octadecyl (C₁₈) columns (Solid-Phase Extraction System, J.T. Baker Chemicals, Pilsburg, NJ), previously rinsed with acidified water. These columns were sequentially washed with acidified water, 15 percent methanol and benzene, and finally eluted with ethylacetate. The ethylacetate fraction was dried at 37°C under N₂ and redissolved in radioimmunoassay (RIA) buffer. PGs were assayed in extracted plasma samples by competitive-binding RIA technique. All assays were performed with New England Nuclear RIA kits.²

PG metabolite levels are expressed as picogram per milliliter. Intra-assay and interassay variability (standard error) was ±3.1 pg/ml and ±6.7 pg/ml, respectively. The accuracy (>99 percent) of the method was evaluated by determining the accuracy of PG spiked into human plasma. The sensitivity of the assay was 10 pg/ml for both 6-keto-PGF₁α and thromboxane B₂.

Statistical analyses of parameter means during baseline, midpoint, and postinfusion of each group were tested using a randomized block analysis of variance (ANOVA) in conjunction with the Student-Neuman-Keuls test.³ A two-way analysis of variance, with repeated measures, followed by a Neuman-Keuls multiple comparisons test, was used to analyze the effects of fast vs slow Intralipid on the studied parameters. In all cases, a p value less than 0.05 was considered indicative of a statistically significant difference.

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**Table 1—Hemodynamic Parameters and Prostaglandin Concentrations during Slow Intralipid Infusion**

<table>
<thead>
<tr>
<th>Intralipid/Slow Infusion</th>
<th>Baseline</th>
<th>Midpoint</th>
<th>After Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂/FIO₂</td>
<td>220 ± 33</td>
<td>171 ± 31</td>
<td>206 ± 34</td>
</tr>
<tr>
<td>Qs/Qr</td>
<td>25.3 ± 5.1</td>
<td>33.8 ± 4.6</td>
<td>23.1 ± 5.2‡</td>
</tr>
<tr>
<td>CO</td>
<td>8.33 ± 0.79</td>
<td>8.25 ± 0.87</td>
<td>7.69 ± 0.74</td>
</tr>
<tr>
<td>MPAP</td>
<td>29.3 ± 3.8</td>
<td>31.3 ± 4.0</td>
<td>25.2 ± 3.5‡</td>
</tr>
<tr>
<td>PAD-PCW</td>
<td>5.5 ± 1.3</td>
<td>5.6 ± 0.9</td>
<td>4.9 ± 0.6</td>
</tr>
<tr>
<td>PVR</td>
<td>125 ± 33</td>
<td>138 ± 50</td>
<td>124 ± 19</td>
</tr>
<tr>
<td>SVR</td>
<td>706 ± 72</td>
<td>711 ± 58</td>
<td>688 ± 72</td>
</tr>
<tr>
<td>PGF₁α</td>
<td>227 ± 28</td>
<td>259 ± 28</td>
<td>188 ± 24‡</td>
</tr>
<tr>
<td>Thromboxane</td>
<td>313 ± 35</td>
<td>300 ± 29</td>
<td>250 ± 37‡‡</td>
</tr>
</tbody>
</table>

*Values are mean ± SE.
†p<0.05 from baseline.
‡p<0.05 from midpoint.

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**Table 2—Hemodynamic Parameters and Prostaglandin Concentrations during Fast Intralipid Infusion**

<table>
<thead>
<tr>
<th>Intralipid/Fast Infusion</th>
<th>Baseline</th>
<th>Midpoint</th>
<th>After Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂/FIO₂</td>
<td>226 ± 26</td>
<td>206 ± 32</td>
<td>223 ± 36</td>
</tr>
<tr>
<td>Qs/Qr</td>
<td>19.7 ± 3</td>
<td>22.7 ± 4.0</td>
<td>19.5 ± 3.2</td>
</tr>
<tr>
<td>CO</td>
<td>6.92 ± 0.67</td>
<td>7.43 ± 0.73</td>
<td>8.04 ± 0.91</td>
</tr>
<tr>
<td>MPAP</td>
<td>22.0 ± 2.2</td>
<td>25.0 ± 2.6</td>
<td>23.8 ± 2.9‡</td>
</tr>
<tr>
<td>PAD-PW</td>
<td>3.6 ± 0.4</td>
<td>4.5 ± 0.5</td>
<td>4.6 ± 0.5</td>
</tr>
<tr>
<td>PVR</td>
<td>94.7 ± 15.5</td>
<td>106.7 ± 10.7</td>
<td>95.7 ± 17.2</td>
</tr>
<tr>
<td>SVR</td>
<td>760 ± 65</td>
<td>1515 ± 831</td>
<td>764 ± 74</td>
</tr>
<tr>
<td>PGF₁α</td>
<td>168 ± 19</td>
<td>293 ± 64</td>
<td>194 ± 22</td>
</tr>
<tr>
<td>Thromboxane</td>
<td>306 ± 42</td>
<td>338 ± 51</td>
<td>240 ± 26‡‡</td>
</tr>
</tbody>
</table>

*Values are mean ± SE.
†p<0.05 from baseline.
‡p<0.05 from midpoint.

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**RESULTS**

The effects of slow Intralipid infusion on the measured hemodynamic parameters and PG concentrations are presented in Table 1. Shunt fraction (Qs/Qr) increased from 25.3 ± 5.1 at baseline to 33.8 ± 4.6 at the midpoint of infusion. After termination of infusion, shunt fraction (Qs/Qr), MPAP, 6-keto-PGF₁α, and thromboxane B₂ concentrations decreased significantly.

In Table 2, the fast Intralipid infusion data are presented. MPAP increased from 22.0 ± 2.2 at baseline to 28.0 ± 2.6 at the midpoint of infusion. Other hemodynamic parameters measured and PG values were not changed significantly from baseline. In the postinfusion period, MPAP returned to baseline. In addition, in the postinfusion period, thromboxane B₂ concentrations decreased significantly from baseline and midpoint levels (Table 2). Other parameters in the postinfusion period were not significantly different from baseline and midpoint.

Figure 1 compares the effects of slow and fast Intralipid infusions on Qs/Qr, MPAP, 6-keto-PGF₁α, and thromboxane B₂. Qs/Qr, at midpoint of infusion, was increased significantly in the slow infusion group compared with the fast infusion group. MPAP, at midpoint of infusion, was increased significantly in the fast infusion group relative to the slow infusion group. The arterial plasma concentrations of 6-keto-PGF₁α and thromboxane B₂, at midpoint of infusion, were not significantly different between the two groups. In the postinfusion period, Qs/Qr was not significantly different between the two groups. MPAP of the fast infusion group remained significantly increased compared with the slow infusion group in the postinfusion period. The 6-keto-PGF₁α levels of the fast infusion group, however, were significantly increased from the slow infusion group in the postinfusion period. Thromboxane B₂ levels were unchanged between the two groups in the postinfusion period. It

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**References**


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can be seen that the systemic plasma concentrations of the vasodilator metabolite (6-keto-PGF1,) and the vasoconstrictor metabolite (thromboxane B2) did not correlate to the observed changes in Qs/QT and MPAP.

**DISCUSSION**

Intralipid contains a high concentration of PG precursor linoleic acid. This precursor can be rapidly converted in vivo into vasodilating, anti-inflammatory PGs (PGE2 and PG12) and vasoconstricting, proinflammatory PGs such as PGF2α and thromboxane A2. The quantity and the type of PGs produced can vary depending on the speed with which PG precursors are administered. Experimental studies have demonstrated that a rapid bolus of IVFE results in increased bronchial and vascular smooth muscle tone, while slow infusion has the opposite effect. During a bolus or rapid infusion, excessive amounts of PG precursors may overwhelm the enzyme systems for PGE2 and PG12, leaving a net increase in PG with vasoconstrictive properties, ie, thromboxane A2. Thus, it is tempting to speculate that one can modulate the type of PGs produced at the lung level by varying the rate of IVFE administration, ie, slow infusion producing vasodilating PGs and fast infusion vasoconstricting PGs.

Several lines of experimental evidence suggest that gas exchange abnormalities associated with IVFE are in part mediated by PGs. Hageman et al have demonstrated, in rabbits with oleic acid–damaged lungs, that Intralipid infusion resulted in decreased PaO2 and increased production of vasodilator PG metabolites (PGE2, 6-keto-PGF1α). Both of these effects were blocked by indomethacin, a PG inhibitor. McKeen et al demonstrated in a sheep model that Intralipid infusion resulted in a substantial increase in MPAP and microvascular pressure with concomitant reduction in PaO2. In addition, these authors demonstrated that indomethacin both prevented and reversed the pulmonary vascular effects of Intralipid infusion.

In our patients, slow IVFE infusion produced a significant increase in Qs/QT at midpoint that returned to baseline at the termination of the infusion. The increased Qs/QT may be due to increased production of endogenous vasodilators. These substances may oppose the existing hypoxic pulmonary vasoconstriction (HPV) response resulting in increased Qs/QT. Similar mechanisms have been proposed for increased Qs/QT in other situations where exogenous vasodilators have been used in patients with preexisting ventilation/perfusion abnormalities. During fast
IVFE infusion, Qs/Qr was unchanged at midpoint of infusion and MPAP was significantly increased. MPAP was unchanged during slow Intralipid administration. These data suggest that slow and fast Intralipid infusions cause pulmonary vasodilation and vasoconstriction, respectively.

During slow infusion, we were unable to demonstrate statistically significant increases in 6-keto-PGF1α levels with the observed increases in Qs/Qr. Again, in the fast infusion group, PG levels at the midpoint of fast Intralipid infusion were not significantly different from baseline. In the slow and fast infusion groups, when the PG substrate was removed during the postinfusion period, hemodynamic and PG metabolite values decreased in parallel (Fig 1).

In conclusion we have demonstrated that slow infusion of IVFE resulted in pulmonary vasodilator response with concomitant increases in Qs/Qr, while fast infusion caused vasoconstriction that increased MPAP without any increases in Qs/Qr. We were unable to demonstrate a cause and effect relationship between plasma levels of the measured PGs and the observed pulmonary hemodynamic response. Clinical implications of this study are not clear at this time. Future investigation may focus on whether IVFE could be used to modulate pulmonary inflammatory response, vasomotor tone, platelet aggregation, and membrane function.

REFERENCES
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