Hemodynamic, Respiratory, and Metabolic Effects of Medium-Chain Triglyceride-enriched Lipid Emulsions Following Valvular Heart Surgery*

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Study: A lipid emulsion containing 10 percent medium-chain triglycerides (MCT) and 10 percent long-chain triglycerides (LCT) was infused at a rate of 1 ml/kg/h (3.3 mg/kg/min) for 2 h, in 12 patients (2 males, 10 females; mean age, 54±3 (SEM) years; range, 34 to 67 years) 24 h after open-heart surgery (mitral valve replacement).

Methods: Hemodynamic factors (pulmonary and radial artery indwelling catheters), oxygen and carbon dioxide partial pressures, oxygen saturation, oxygen delivery and consumption, and intrapulmonary shunt fraction were obtained before, during, and after lipid infusion (for 2 h), at 30-s intervals, along with some metabolic indexes (triglycerides, free fatty acids, glucose, insulin, lactate, acetooacetate).

Results: No statistically significant changes in heart rate, cardiac index, systemic and pulmonary pressures and resistances, central venous and pulmonary capillary pressures, or arterial oxygen partial pressure were observed during infusion. Arterial carbon dioxide partial pressure values were constantly reduced throughout and after the end of lipid infusion, as compared with baseline values, while oxygen consumption was increased significantly without any change in oxygen delivery. No adverse effects on intrapulmonary shunt fraction were observed. Statistically significant increases of triglycerides, free fatty acids, acetooacetate and insulin (peak values at end of the lipid infusion) were found in comparison with baseline values. Plasma glucose increased significantly during lipid infusion and remained higher than baseline values until the end of the study. Lactate levels were unchanged, except for a slight decrease at the end of the study, without any derangement of acid-base equilibrium. Neither arrhythmias nor adverse clinical reactions were observed as a consequence of lipid infusion.

Conclusion: Fat emulsions containing both MCT and LCT, when given at 3.3 mg/kg/min for 120 min following valvular heart surgery, do not exert negative cardiopulmonary effects, and could represent a source of rapidly metabolized substrates.

(Chest 1994; 106:1660-67)

Intravenous fat emulsions (IVFE) are frequently utilized as a component of parenteral nutrition in the critically ill. However, several experimental and clinical studies have documented cardiopulmonary function alterations associated with IVFE administration: lung function derangements usually have involved decreased oxygenation\(^1\)\(^-\)\(^9\) and variable increases of intrapulmonary shunt fraction,\(^9\)\(^-\)\(^13\) while cardiac and circulatory alterations have been characterized by negative inotropic effects with reduced cardiac output\(^11\)\(^-\)\(^12\) as well as by increased pulmonary pressures and resistances.\(^8\)\(^-\)\(^10\)\(^-\)\(^13\)\(^-\)\(^15\)

Understanding the potential cardiopulmonary complications of IVFE is of primary interest in clinical nutrition, since there is a widespread indication for increasing the proportion of the lipid component of the nonprotein caloric supply in particular in patients with respiratory and/or cardiac illness.\(^16\)\(^,\)\(^17\)

Currently available IVFE are derived from soybean and/or safflower oils and contain long-chain (20 carbon atoms) omega-6 and omega-3 polyunsaturated fatty acids esterified with glycerol to form long-chain triglycerides (LCT).\(^18\) The composition in fatty acids of lipid emulsions is considered a key
factor in determining cardiopulmonary effects of IVFE.\textsuperscript{19,20} Long-chain polyunsaturated fatty acids serve, in fact, as precursors of prostaglandins and thromboxanes. These eicosanoids are known to exert composite effects on vascular tone—in particular on the pulmonary vascular bed—with possible consequences on pulmonary gas exchange as well.\textsuperscript{19,20}

The search for alternative lipid emulsions has led to the formulation of new lipid emulsions, characterized by the partial replacement of LCT with medium-chain triglycerides (MCT). The latter are semi-synthetic triacylglycerols obtained from hydrolysis of coconut oil and fractionation into free fatty acids (FFA) with 6 and 12 carbon atoms (mainly C8 and C10 fatty acids). Because MCT do not interfere with eicosanoid synthesis and availability, their presence as components of IVFE could be associated with reduced or no adverse cardiopulmonary effects, even in patients with respiratory or cardiac illness, or both. Moreover, in the critically ill patient, the use of MCT could provide many metabolic benefits, such as lesser carnitine requirements for mitochondrial entry, rapid metabolism to readily available fuels (acetylCoA and ketone bodies), no needs for storage in adipose tissue and no deposition in the reticuloendothelial system.\textsuperscript{21}

A physical mixture of MCT and LCT is currently available for clinical use, and the present study was thus designed to evaluate its cardiopulmonary and metabolic effects. To this purpose, during the administration of the MCT/LCT IVFE in the early postoperative period following open-heart surgery for mitral valve disease, clinical, respiratory, hemodynamic, and metabolic monitoring was performed in a group of patients in the heart surgery ICU.

\section*{Patients and Methods}

\textbf{Patients}

Subjects scheduled for elective cardiac surgery for mitral valve disease at the Heart Surgery Division were considered eligible for the study. Patients were evaluated 24 h after the end of the operative procedures in the heart surgery ICU: they were excluded from the study if a stable postoperative course was not demonstrated on the basis of respiratory and hemodynamic monitoring and/or they were not extubated. Moreover, the presence of any of the following conditions (before or after surgery) was considered an exclusion criterion: preoperative chronic renal failure, diabetes and dyslipidemia, acute perioperative myocardial infarction, postoperative cardiac index less than 2.2 L/min, acute renal failure, fever (>38°C), and nonsteroidal anti-inflammatory drug administration. Twelve patients (functional class II-III New York Heart Association classification) were selected. There were ten females and two males, with a mean age of 54 years (3.2 SEM; range, 43 to 67 years). Explanation as to the nature, purpose, and potential risks of the study was given to all patients; written informed consent was obtained from each participant for all procedures before surgery. The study was conducted according to the principles embodied in the Declaration of Helsinki.

\section*{Study Protocol}

Routine hemodynamic and respiratory monitoring was performed according to institutional protocols: on the day of the operative procedure, in the operating room, an indwelling catheter was inserted into the radial artery for monitoring and sampling; after anesthesia induction, a 7F quadruple lumen, thermistor-tipped, flow-directed catheter (Sorensen Research, Abbott, Salt Lake City, Utah), was advanced into the pulmonary artery via the right jugular vein. Nonpulsatile cardiopulmonary bypass was carried out using a roller pump and disposable bubble oxygenator. Flow rates were maintained at 2.2 L/min/m\textsuperscript{2} during cardiopulmonary bypass; mean arterial pressure was monitored and maintained between 60 and 80 mm Hg. Potassium cardioplegic arrest during the period of aortic clamping was used.

Lipids under the form of a 20 percent MCT/LCT physical mixture (Lipofundin MCT, B. Braun, Milan, Italy) were given at a rate of 1 ml/kg/h (3.3 mg/kg/min) for 2 h. Lipofundin MCT contains 100 g/L of MCT and 100 g/L of soybean LCT; 46 percent of fatty acids have a chain length of C6 to C10, and 54 percent have a chain length of C16 to C18 (egg yolk phosphatides as emulsifiers).

Hemodynamic monitoring, arterial and mixed venous blood gas levels, and arterial oxygen saturation (SaO\textsubscript{2}) were obtained before the infusion, at 30, 60, 90, and 120 min during the infusion, and at 30, 60, and 120 min after the end of the infusion (washout period). At the same intervals, blood samples were taken for metabolic index measurement (triglycerides, FFA, acetocetate, glucose, insulin, lactate).

Institutional protocols for the postoperative management of the patients studied were not altered during the period of the study; as a part of the routinely scheduled drugs regimen, mini-dose subcutaneous administration of heparin (5,000 IU three times a day) was given. Moreover, a 10 percent D-glucose infusion was started at arrival in the ICU at a rate of 33 ml/h (about 0.75 mg/kg/min).

\section*{Measurements, Analytical Procedures, and Calculations}

Arterial and mixed venous pH, P\textsubscript{CO\textsubscript{2}} and P\textsubscript{O\textsubscript{2}} values were measured in duplicate with a blood gas analyzer (IL BGE, Instrumentation Laboratories, Lexington Mass). The SaO\textsubscript{2} and hemoglobin concentrations were measured with a cooximeter (IL 482). Cardiac output was measured by the thermodilution method with an integrated cardiac output computer (Sirecust 901, Siemens, Germany), from the mean of three electronically integrated decay curves generated after the administration of 10 ml of room temperature saline solution injected via the proximal lumen of the pulmonary artery catheter. Cardiac index (CI), systemic vascular resistances index, mean arterial pressure, arterial oxygen content, mixed venous oxygen content, intrapulmonary shunt fraction, oxygen consumption, and delivery were calculated on the basis of standard formulas, as previously described.\textsuperscript{22}

Plasma triglycerides were measured by an enzymatic method.\textsuperscript{23} FFA were measured enzymatically using the acylCoA-synthetase method, which measures fatty acids of various chain length.\textsuperscript{24} Acetocetate was measured enzymatically on blood samples deproteinized with perchloric acid,\textsuperscript{25} plasma glucose was measured by a Technicon CHEM1 automated glucose analyzer; plasma insulin concentration, by an enzyme-linked immunosorbent assay method with a commercially available kit (Enzymun-Test Insulin, Boheringer Mannheim GmbH, Germany); and lactate, by the ACA IV lactate analyzer (DuPont, Wilmington, Del).
Table 1—Effects of 20 Percent Medium- and Long-Chain Tryglyceride Lipid Emulsion Infusion on Hemodynamic Indexes*

<table>
<thead>
<tr>
<th>Hemodynamic Indexes</th>
<th>Baseline</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>30 Post-Infusion</th>
<th>60 Post-Infusion</th>
<th>120 Post-Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI, (L/min/m²)</td>
<td>3.38 ± 0.15</td>
<td>3.23 ± 0.19</td>
<td>3.26 ± 0.14</td>
<td>3.38 ± 0.46</td>
<td>3.37 ± 0.46</td>
<td>3.45 ± 0.26</td>
<td>3.45 ± 0.26</td>
<td>3.51 ± 0.15</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>82 ± 3</td>
<td>84 ± 3</td>
<td>84 ± 3</td>
<td>84 ± 2</td>
<td>80 ± 3</td>
<td>79 ± 3</td>
<td>79 ± 2</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>Systemic vascular resistance index, dynes/cm²·m²</td>
<td>1,778 ± 123</td>
<td>1,919 ± 148</td>
<td>1,857 ± 111</td>
<td>1,908 ± 112</td>
<td>1,715 ± 112</td>
<td>1,671 ± 117</td>
<td>1,681 ± 114</td>
<td>1,607 ± 116</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>9 ± 3</td>
<td>10 ± 3</td>
<td>10 ± 3</td>
<td>10 ± 4</td>
<td>9 ± 4</td>
<td>10 ± 4</td>
<td>9 ± 4</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
<td>15 ± 1</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>29 ± 2</td>
<td>29 ± 2</td>
<td>28 ± 2</td>
<td>29 ± 2</td>
<td>28 ± 2</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index, dynes/cm²·m²</td>
<td>364 ± 60</td>
<td>384 ± 54</td>
<td>385 ± 58</td>
<td>389 ± 58</td>
<td>396 ± 46</td>
<td>326 ± 59</td>
<td>301 ± 54†</td>
<td>290 ± 53†</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM.

p<0.05 vs baseline values (paired data Student’s t test).

Statistics

For any measured variable, the statistical significance of changes in mean values over time was assessed by one-way analysis of variance for repeated measures, and when an “F” value indicated a difference, the Student’s t test for paired samples was used to determine the significance of variations from the baseline values for any point in time. Statistical significance was set at a probability value of less than 0.05. Values are reported as mean ± SEM.

Results

No adverse clinical effects were evident during or following lipid administration. No changes in CI, systemic or pulmonary pressures, and resistances were observed during IVFE infusion (Table 1); a slight but statistically significant decrease of both systemic and pulmonary vascular resistances at the end of the washout period in comparison to values before the infusion was noted; no statistically significant alterations in central venous pressure and pulmonary capillary wedge pressure were demonstrated during the entire period of investigation. Arterial oxygen partial pressure and SaO₂ did not change

Table 2—Effects of 20 Percent Medium- and Long-Chain Tryglyceride Lipid Emulsion Infusion on Pulmonary Gas Exchange, Intrapulmonary Shunt, and Systemic Oxygen Utilization Values*

<table>
<thead>
<tr>
<th>Pulmonary Factors</th>
<th>Baseline</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>30 Post-Infusion</th>
<th>60 Post-Infusion</th>
<th>120 Post-Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂, mm Hg</td>
<td>73 ± 3</td>
<td>76 ± 4</td>
<td>76 ± 4</td>
<td>75 ± 5</td>
<td>75 ± 4</td>
<td>75 ± 4</td>
<td>70 ± 3</td>
<td>70 ± 3</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>94 ± 0.8</td>
<td>94 ± 0.7</td>
<td>94 ± 0.9</td>
<td>94 ± 0.8</td>
<td>94 ± 0.7</td>
<td>94 ± 0.8</td>
<td>93 ± 0.5</td>
<td>93 ± 0.5</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation, %</td>
<td>68 ± 1.9</td>
<td>64 ± 1.9†</td>
<td>63 ± 1.9†</td>
<td>63 ± 2.3†</td>
<td>64 ± 2.3†</td>
<td>65 ± 2.5†</td>
<td>66 ± 1.8</td>
<td>66 ± 1.2</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>38.1 ± 1.5</td>
<td>37.0 ± 1.1†</td>
<td>36.7 ± 1.5†</td>
<td>36.4 ± 1.3†</td>
<td>35.4 ± 1.3§</td>
<td>35.1 ± 1.2§</td>
<td>34.6 ± 1.1§</td>
<td>35.1 ± 1.3§</td>
</tr>
<tr>
<td>Intrapulmonary shunt fraction, %</td>
<td>18.6 ± 1.8</td>
<td>16.6 ± 1.8</td>
<td>15.5 ± 1.7§</td>
<td>16.8 ± 1.6</td>
<td>16.1 ± 1.4</td>
<td>17.2 ± 1.5</td>
<td>18.9 ± 1.2</td>
<td>17.9 ± 1.4</td>
</tr>
<tr>
<td>Systemic oxygen consumption, ml/min/m²</td>
<td>122 ± 4</td>
<td>133 ± 5†</td>
<td>140 ± 5†</td>
<td>141 ± 7†</td>
<td>140 ± 7†</td>
<td>135 ± 6†</td>
<td>132 ± 6†</td>
<td>134 ± 5†</td>
</tr>
<tr>
<td>Oxygen delivery, ml/min/m²</td>
<td>445 ± 21</td>
<td>425 ± 23</td>
<td>429 ± 17</td>
<td>442 ± 19</td>
<td>444 ± 16</td>
<td>453 ± 22</td>
<td>451 ± 22</td>
<td>460 ± 17</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM.

†Probability less than 0.01 vs baseline values (paired data, Student’s t test).

‡Probability less than 0.05 vs baseline values (paired data, Student’s t test).

§Probability less than 0.001 vs baseline values (paired data, Student’s t test).
from baseline levels during the course of the study (Table 2); PaCO₂ was constantly reduced throughout and after the end of lipid infusion; a statistically significant increase in oxygen consumption was found during lipid administration beginning from 30 min after the infusion was started, while oxygen delivery values remained stable; no adverse effects on intrapulmonary shunt fraction were documented during the study.

During lipid infusion, the plasma concentration of triglycerides and FFA significantly increased from baseline levels (Table 3); peak value concentrations were reached between 90 and 120 min of infusion for both triglycerides and FFA levels, with a rapid drop after the infusion was stopped. Peak values for acetoacetate were measured at the end of IVFE infusion. Both glucose and insulin levels increased significantly during lipid infusion, but while insulin returned to baseline values during the washout period, glucose remained elevated, with peak values at the end of the washout period.

**DISCUSSION**

Several advantages derive from the use of lipids in parenteral nutrition: IVFE represent an isotonic source of energy with high caloric density; their use as a noncarbohydrate fuel may reduce the adverse effects of excessive glucose administration, as well as provide both essential fatty acids and fat-soluble vitamins. Moreover, preferential fat utilization has been demonstrated in critically ill patients, with nitrogen retention comparable to that obtained with glucose and reduced metabolic production of CO₂.

The IVFE based solely on LCT have a number of disadvantages, including documented negative effects on cardiopulmonary function: in experimental studies, high-dose IVFE infusion was in fact associated with a reduction of oxygenation, negative inotropic effects, and increased pulmonary artery pressures.

An important role in the pathogenesis of respiratory and hemodynamic effects of IVFE has been attributed to their potential interference with the synthesis and availability of substances acting on the pulmonary vascular bed. The C₂₀ polyunsaturated fatty acid contained in IVFE based solely on LCT are in fact the biosynthetic precursors of the eicosanoids—which include prostaglandins and thromboxanes—substances known to exert composite effects on vascular tone. It has thus been suggested that the IVFE-associated negative effects on cardiopulmonary function could be attributed to the effects of IVFE metabolism products.

Fat emulsion administration has been found to increase the prostaglandin concentration in plasma. A key point in the experimental studies was that respiratory effects, which were unrelated to the degree of lipemia, were prevented by eicosanoid synthesis inhibition. Indomethacin pretreatment in fact prevented the PaO₂ reduction consequent to IVFE administration in both healthy and injured lungs. Moreover, in a recent experimental study, not only was a close relationship found between the levels of vasoactive eicosanoid, such as thromboxane-β₂, and the observed increase in pulmonary vascular resistances, but also vascular tone alterations were prevented by the administration of a thromboxane β₂ antagonist.

Many clinical studies in both healthy subjects and critically ill patients have confirmed the IVFE-related changes in cardiopulmonary function demonstrated in the experimental setting. Reduction in PaO₂, alveolar-arterial oxygen gradient, and carbon dioxide diffusion were found in healthy volunteers and in patients with atherosclerotic heart.
Following cardiac surgery, short-term, low-dose infusion of IVFE (1.1 mg/kg/min for 10 min to 2.35 mg/kg/min for 1 hr) had no effect on hemodynamic status or respiratory function, while higher doses (5.25 mg/kg/min for 2 hr) were associated with a decrease in cardiac output. In the latter study, a dose-response effect was shown for the decrease in cardiac output, and it was attributed to a myocardial depressive effect of IVFE. The possibility of a direct effect of IVFE administration on cardiac function cannot be excluded, since a negative inotropic effect with a parallel increase of peripheral vascular resistances has been shown after LCT infusion in an isovolumetric left heart canine preparation. Free fatty acids can significantly affect myocardial cell metabolism, and postulated mechanisms include inhibition of various aspects of membrane function, such as mitochondrial adenosine 5'-triphosphate-adenosine 5'-diphosphate translocase, the sodium/potassium pump, and phospholipid cycles.

The adverse effects of IVFE on cardiopulmonary function in human clinical beings are even more evident in the case of preexisting respiratory illness: in this condition, IVFE administration is in fact associated with decreased oxygenation, increased intrapulmonary shunt fraction, and increased mean pulmonary artery pressures and resistances; in particular, sepsis, and/or adult respiratory distress syndrome, are linked to more severe pulmonary vascular tone derangement and gas exchange alterations after IVFE administration.

No effects on either lung function or hemodynamic status were demonstrated in the group of patients we studied. Two factors could have accounted for this finding. First, since MCT-derived fatty acids are not eicosanoid precursors, less interference on both cardiac function and pulmonary vascular tone is to be expected as a result of the infusion of this component of the IVFE. Second, even though the total IVFE infusion rate was 3.3 mg/kg/min (equivalent to the mean infusion rate needed to give 500 ml of a 20 percent IVFE infusion in 8 h), the different fatty acid composition of the IVFE utilized—as compared with IVFE based solely on LCT—effectively reduced the infusion rate of the LCT component to about 1.65 mg/kg/min. The lipid infusion rate is thought to be an important determinant of the cardiopulmonary effects of IVFE, since it could elicit the predominant pathway of IVFE metabolism: it has been hypothesized that rapid infusion or bolus administration could lead to a net increase in vasoconstrictive eicosanoids (both prostaglandins and thromboxanes), as the enzymatic pathways for vasodilatory eicosanoids could be overwhelmed. Unfortunately, no definitive data are currently available on this topic in human beings: even though this hypo-

desis could account for the increase in pulmonary vascular resistances and pressures observed during high infusion rates in the clinical setting, a recent study on the effects of fast vs slow IVFE infusion on pulmonary hemodynamics and eicosanoid metabolism in ARDS patients failed to demonstrate a cause and effect relationship between plasma levels of both prostaglandins and thromboxanes and the observed pulmonary hemodynamic response.

The infusion of MCT-enriched lipid emulsion was associated with several metabolic changes in our patients.

Plasma triglyceride levels rose during lipid administration and reached a steady state at 60 to 120 min of the infusion, with a parallel FFA increase. Medium-chain fatty acids are more rapidly oxidized as compared with the other saturated fatty acids, and their administration is associated with an increase of both hepatic ketogenesis and plasma ketone body concentration. Ketosis was not an important metabolic problem in the patients studied. Since a glucose infusion (0.75 mg/kg/min) was maintained during the study, we cannot exclude that it could have limited the potential rise of ketone body levels, by increasing pyruvate (and oxaloacetate) availability, thus facilitating ketone body utilization through the Krebs cycle. In any case, ketone bodies produced in the liver represent an energetic source for many tissues (heart, central nervous system, muscles, gastrointestinal tract); in our patients, acetocetate, which is representative of ketone body synthesis, fell rapidly after the end of the infusion, suggesting rapid tissue utilization. Moreover, oxygen consumption was increased by about 15 percent above baseline values during MCT/LCT infusion, a finding consistent with the hypothesis of obligatory use of medium-chain fatty acids as a fuel, since storage is not a potential metabolic pathway. On the basis of this evidence, previous studies have demonstrated that resting energy expenditure, oxygen consumption, carbon dioxide production, and calculated fat oxidation were increased during MCT/LCT infusion but not during the administration of IVFE containing LCT only or disodium sebacate, the sodium salt of sebacic acid, a medium-chain dicarboxylic acid. From these studies, it can be inferred that the increased thermogenesis observed in the course of parenteral nutrition containing MCT is most likely due to increased fat oxidation; from this point of view, skeletal muscle seems to play an important role, both in experimental and in clinical conditions. An important finding in our study was that while oxygen consumption increased during IVFE infusion, no changes in systemic oxygen delivery were found, i.e., the increased metabolic requirements for FFA utilization were met through the activation of peripheral mecha-
organisms which increase tissue oxygen extraction. This could be of particular interest in parenteral nutrition of patients with cardiac illness or reduced cardiac reserve, or both; artificial nutrition in these clinical conditions, in particular if malnutrition coexists, could be associated with an increased risk of refeeding syndrome, which encompasses many adverse effects on cardiovascular and respiratory systems.

Particular attention has been paid in our study to carbohydrate metabolism, since fatty acids are known to exert composite effects on glucose metabolism. While no clinically important alterations of plasma glucose levels have been demonstrated during and after MCT/LCT infusion in healthy subjects, hyperglycemia has been documented during MCT/LCT administration in critically ill patients with trauma or sepsis, or both, and in acute renal failure. Also in our patients, the plasma glucose value increased during MCT/LCT infusion, reaching a steady state between 60 and 120 min of the infusion; thereafter, levels were further increased and remained high during the washout period. Plasma insulin levels, which were still high at baseline conditions, increased further during lipid administration but promptly returned to baseline values after the end of lipid administration.

Several mechanisms could contribute to hyperglycemia during the IVFE infusion; they are linked to an impairment of both oxidative and nonoxidative pathways of intracellular glucose disposal, as well as to an increased glucose production.

Elevations of plasma FFA due to triglyceride administration are known to inhibit glucose oxidation, as the consequence of substrate competition between glucose and FFA as oxidative fuels: as demonstrated by Randle et al in his original work, the addition of fatty acids to the perfusion medium of isolated rat hearts and hemidiaphragms was able to inhibit glucose transport, anaerobic utilization, and oxidation. While in healthy subjects in basal conditions, IVFE infusion induces hyperglycemia only if the compensatory insulin release (driven by a direct effect of FFA on beta-cell or mediated by the increasing glucose levels) is blocked by somatostatin infusion; the cycle noted by Randle et al has been demonstrated to be operative in man under several experimental and clinical conditions, which, like our experimental setting, are characterized to be high-insulin, high-glucose turnover states. Moreover, a constant glucose infusion was performed in our patients; as shown by Wolfe and colleagues, when the rate of glucose uptake is constant, increases in circulating FFA also may affect total glucose oxidation by suppressing glycojen oxidation.

The inhibition of glycogen synthesis, another mechanism involving nonoxidative glucose utilization, could have also contributed to the resistance to insulin-mediated glucose utilization associated with IVFE administration: glycojen synthesis is the most important nonoxidative glucose disposal pathway, and the inhibition of glucose storage observed during the experimental rise of FFA and in obesity, appears to be a quantitatively important phenomenon.

Finally, IVFE administration could have determined hyperglycemia through increased hepatic production of glucose. Free fatty acids in fact stimulate gluconeogenesis from lactate, pyruvate, and alanine in vitro conditions; multiple biochemical mechanisms are probably involved, which include acetylCoA generation from FFA, activation of pyruvate carboxylase, inhibition of pyruvate dehydrogenase and generation of adenosine 5'-triphosphate and nicotinamide adenine dinucleotide (reduced form). An increased gluconeogenic effect of FFA has been demonstrated in healthy subjects made moderately hyperglycemic or under pancreatic clamp with insulin and glucagon replacement at basal levels. Increased gluconeogenesis during lipid infusion also could be partially due to glycerol contained in IVFE; however, under this condition, glycerol-induced substrate effect explains only a variable percentage (40 to 70 percent) of the increased gluconeogenic flux observed. In any case, the increase in plasma glucose levels demonstrated in our patients during MCT/LCT infusion should not cause clinical problems; it seems prudent, however, to monitor glucose levels during parenteral nutrition with glucose and IVFE.

In conclusion, the results obtained in our study suggest that the administration of an MCT-enriched IVFE at 3.3 mg/kg/min for 120 min is not associated with any adverse clinical or metabolic effects or with alterations of either hemodynamic status or lung function in heart surgery patients evaluated in the early postoperative phase following mitral valve replacement; thus, at least in this clinical condition, IVFE based on a physical mixture of MCT and LCT could represent an advantageous source of substrates.

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CHEST / 106 / 6 / DECEMBER, 1994 1665

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Effects of Lipid Emulsions After Valvular Heart Surgery (Fiaccadori et al)
American Board of Internal Medicine

1995 Certification, Recertification and Qualifying Examinations in Critical Care Medicine

Registration Period: January 1 - April 1, 1995
Examination Date: November 9, 1995

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