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Fat emulsions containing medium chain triglycerides in patients with sepsis syndrome: effects on pulmonary hemodynamics and gas exchange

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Abstract. Fat emulsions containing medium chain triglycerides (MCT) have recently been introduced into clinical practice as a component of total parenteral nutrition. Since several authors reported increased pulmonary artery pressure and impaired gas exchange during intravenous (i.v.) fat use, in particular in septic patients, we studied the pulmonary hemodynamic and gas exchange effects of i.v. fat containg MCT and long chain triglycerides (LCT) in patients with sepsis syndrome. As the effects of fat emulsions have been attributed to increased formation of prostanoids, the production of thromboxane A_2 and prostacyclin was investigated by the determination of urinary thromboxane B_2 and 6-keto-prostaglandin $F_{2\alpha}$, respectively. The i.v. fat use did not induce any alterations in pulmonary hemodynamics and gas exchange, the distribution of ventilation and perfusion nor urinary prostaglandin content. We conclude that fat emulsions containing MCT induce little alterations in pulmonary hemodynamics and gas exchange. This result is probably due to reduced prostaglandin formation because fat emulsions containing MCT provide less prostaglandin precursors than pure LCT emulsions.

Key words: Sepsis syndrome – Fat infusion – Medium chain triglycerides – Prostaglandin – Ventilation/perfusion distributions

Intravenous fat emulsion are frequently administered as a metabolic fuel to critically ill patients receiving total parenteral nutrition. Recent reports have emphasized increased pulmonary vascular pressures [1, 2] associated with disturbances of pulmonary gas exchange during lipid infusions, the latter being caused by a maldistribution of ventilation and perfusion [1, 3]. These effects were amplified by the presence of sepsis [1, 2] and, therefore, intravenous use remains controversial in septic patients [4].

Recently, fat emulsions containing medium chain triglycerides have been introduced into clinical practice [5, 6] since medium chain fatty acids are metabolized more rapidly than long chain fatty acids [7]. Furthermore, these fat emulsions contain less linoleic, linolenic and arachidonic acid, precursors of prostaglandins and other eicosanoids. These differences may be important because a major contribution to the gas exchange effects of intravenous fat use is attributed to increased production of prostaglandins (thromboxane A_2, prostacyclin) [8–10] since fat emulsions provide precursors of prostaglandins [11].

The aim of our study was to investigate the pulmonary vascular and gas exchange effects of an infusion with fat emulsions containing medium chain triglycerides in patients with the sepsis syndrome receiving total parenteral nutrition. To explain any gas exchange alterations induced by the fat infusion we studied its effects on the distribution of ventilation and perfusion ($\dot{V}_A/\dot{Q}$) together with the production of eicosanoids.

Methods

Nine consecutive patients receiving total parenteral nutrition who met the criteria for the diagnosis of sepsis syndrome [12] were selected for this study. The patient's age, sex, diagnosis, and outcome are presented in Table 1. Their lungs were mechanically ventilated via an endotracheal tube using a volume-cycled ventilator (EV-A, Dräger, Lübeck, FRG)

Table 1. Clinical characteristics of the patients

Patient	Sex/age	Diagnosis	Outcome
F.T.	M/62	Aorto-coronary bypass, pneumonia	Survived
H.G.	M/46	Bowel perforation, ARDS	Died
K.L.	M/72	Coronary artery bypass graft, aortic valve replacement, pneumonia	Survived
K.R.	M/78	Ruptured abdominal aortic aneurysm, bowel ischemia	Died
P.W.	M/19	Multiple trauma	Survived
H.O.	M/65	Mesenteric infarction	Died
F.K.	M/52	Oesophageal resection	Survived
K.L.	F/57	Oesophageal resection	Survived
H.V.	M/46	Multiple trauma, abdominal contusion	Survived

with tidal volumes of 12–15 ml/kg body weight, respiratory rates of 8–11 breaths/min, and 8–12 cmH_2O of PEEP. The mean FiO_2 was 0.38 (range 0.30–0.60). For monitoring and continuous pressure recording a thermodilution pulmonary artery (model 93A-43H-7.5F, Edwards Laboratories, Ternat, Belgium) and radial artery catheters had been inserted. The patients were sedated with a continuous intravenous infusion of fentanyl and midazolam. No corticosteroids or non-steroidal anti-inflammatory drugs were administered within 24 h of the study. The study was conducted according to the principles embodied in the Declaration of Helsinki.

The following measurements were obtained: 1) tidal volume and minute ventilation using a calibrated spirometer (model VM 90, Bourns Inc., Riverside, CA); 2) FiO_2 of a gas sample from the inspiratory limb of the ventilator (ABL 30, Radiometer, Copenhagen); 3) arterial (a) and mixed venous ($\bar{v}$) pH, PO_2, and PCO_2 (ABL 30); 4) total hemoglobin and hemoglobin oxygen saturation by spectrophotometry (OSM 2 Hemoximeter, Radiometer); 5) systemic and pulmonary vascular pressures (Combitrans transducers, Braun, Melsungen, FRG); and 6) cardiac output using a thermodilution cardiac output computer (Edwards model REF-3), the values reported being the mean of five injections of 0 °C saline randomly obtained during the respiratory cycle. The pressure tracings and a continuous ECG were recorded on a VP 95 recorder (Seikosha, Japan).

Systemic and pulmonary vascular resistance indexes and oxygen uptake were calculated using standard formulae, and venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) was computed with the Berggren equation (13) after derivation of the alveolar PO_2 with the alveolar gas equation.

Continuous ventilation-perfusion ($\dot{V}_A/\dot{Q}$) distributions were determined using the multiple inert gas elimination technique of Wagner et al. (14) as described previously (15). A computer assisted analysis allowed estimation of intrapulmonary shunt ($\dot{Q}_S/\dot{Q}_T$, i.e. $\dot{V}_A/\dot{Q} < 0.005$), low $\dot{V}_A/\dot{Q}$ areas ($0.005 < \dot{V}_A/\dot{Q} < 0.1$) and inert gas dead space ($\dot{V}_D/\dot{V}_T > 100$). Since blood lipid levels may influence the partition coefficients of halothane and sulphur hexafluorid (16), the solubilities of the inert gases were measured both before and during the fat infusion. The mean residual sum of squares was 3.71 ± 3.81, indicating compatibility between the measured inert gas data and the calculated distributions (14). In addition, the arterial-alveolar partial pressure differences normalized for the mixed venous partial pressures, i.e. the retention minus the alveolar excretion, were plotted against the solubility for each gas [15, 17].

Serum triglyceride levels were measured with a commercially available enzymatic test kit (Testomat-Triglyceride, Behring, Berlin, FRG). Changes in the generation of prostacyclin (PGI_2) and thromboxane (TxA_2) were assessed in terms of urinary excretion of the stable hydrolysis products 6-keto-prostaglandin $F_{2\alpha}$ (6-keto-$PGF_{2\alpha}$)and thromboxane B_2 (TxB_2), respectively. The data are referred to ng/g creatinine. The concentrations of these compounds were measured by radioimmunoassay as described previously [18]. Normal values for urinary 6-keto-$PGF_{2\alpha}$ and TxB_2 excretion are 600 and 350 ng/g creatinine, respectively in our laboratory.

Protocol

Two successive sets of measurements were obtained at levels of PEEP and FiO_2 which were not changed from the maintenance values used before the study. Data were always collected after 30 min had elapsed with stable hemodynamic conditions, i.e. unchanged vascular pressures and cardiac output. The control data acquisition took place 30 min before starting the fat infusion. The fat emulsion consisted of 10 g/10 ml medium and long chain triglycerides each. The dosage rate of the fat infusion was 0.150 g/kg·h. After 4 h of this infusion equivalent to a total dose of about 50 g i.v. a second set of data was obtained. In addition to these two samples further urine samples were taken for prostaglandin analysis after 2 h of fat administration.

Statistical evaluation

The measurements in the control period and during fat infusion were compared using a non-parametric Wilcoxon signed rank test for paired data. Significance was assumed if $p < 0.05$.

Results

The intravenous fat use significantly enhanced the triglyceride levels from 179 ± 97 to 394 ± 181 mg/100 ml ($p < 0.001$, Fig. 1). These increased triglyceride concentrations were not, however, associated with any change in the prostacyclin or thromboxane production as assessed by the urinary levels of 6-keto-$PGF_{2\alpha}$ (Fig. 2, right panel) and TxB_2 (Fig. 2, left panel).

Table 2 summarizes the hemodynamic and gas exchange data in the control period and during the lipid infusion. The intravenous fat administration did not cause any significant alterations in systemic or pulmonary hemodynamics. The respiratory gas exchange data remained unchanged as well. The pulmonary gas exchange was analyzed using the multiple inert gas elimination technique, the results of which are summarized in Table 3. There was no change in the shunt fraction ($\dot{Q}_S/\dot{Q}_T$), perfusion of lung regions with low $\dot{V}_A/\dot{Q}$ ratios, or in dead space ($\dot{V}_D/\dot{V}_T$). These results are underscored by the difference between the retention and the alveolar excretion of the inert gases: when plotted against the inert gas solubilities (Fig. 3) the curves for the control period and those during fat infusion are virtually identical.

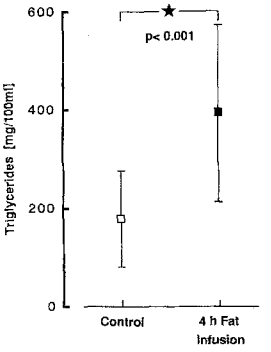

Fig. 1. Triglyceride levels in the control period and at 4 h of fat infusion. Data are presented as mean±SD

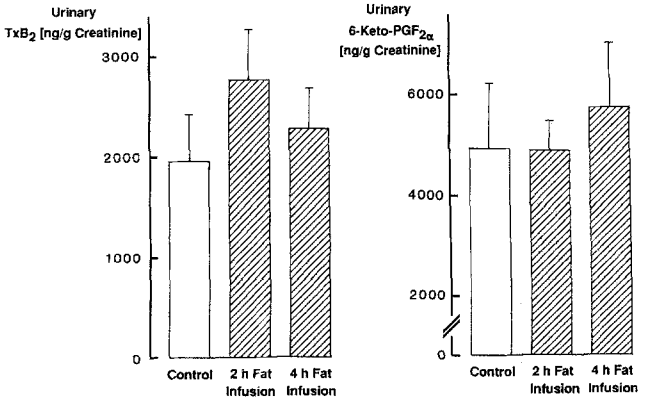

Fig. 2. Urinary thromboxane B2 (TxB_2, *left panel*) and 6-ketoprostaglandin $F_{2\alpha}$ (6-keto-$PGF_{2\alpha}$, *right panel*) in the control phase and at 2 and 4 h of fat infusion, respectively. Data are presented as mean±SD. Note that the control values were 3 times the normal for TxB_2 and 5 times the normal for 6-keto-$PGF_{2\alpha}$. No statistically significant changes occurred during the fat infusion

Table 2. Hemodynamic and gas exchange responses to the fat infusion ($n = 9$, mean ± SD)

	Control	Fat infusion
HR 1/min	119 ± 13	110 ± 10
SAP mmHg	80 ± 21	79 ± 9
PAP mmHg	25 ± 6	26 ± 8
RAP mmHg	12 ± 3	12 ± 4
PAOP mmHg	13 ± 4	12 ± 3
CI $l \cdot min^{-1} \cdot m^{-2}$	4.9 ± 1.8	5.3 ± 1.6
PaO_2 mmHg	104 ± 38	92 ± 17
$PaCO_2$ mmHg	41 ± 4	43 ± 3
$A\bar{V}DO_2$ ml·(100 ml)$^{-1}$	3.1 ± 1.1	3.3 ± 0.5
$\dot{Q}_{VA}/\dot{Q}_T$ %	21 ± 7	23 ± 7

HR = heart rate, SAP = mean systemic arterial pressure, PAP = mean pulmonary artery pressure, RAP = right atrial pressure, PAOP = pulmonary artery occlusion pressure, CI = cardiac index, PaO_2 = arterial PO_2, $PaCO_2$ = arterial PCO_2, $A\bar{V}DO_2$ = arterio-mixed venous oxygen content difference, $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture.
Note that there were no statistically significant differences between the control period and the fat infusion

Table 3. Inert gas elimination data ($n = 9$, mean ± SD)

	Control	Fat infusion
$\dot{Q}_S/\dot{Q}_T$ %	18 ± 8	17 ± 9
low $\dot{V}_A/\dot{Q}$ %	7 ± 7	4 ± 5
$\dot{V}_D/\dot{V}_T$ %	29 ± 9	26 ± 7

$\dot{Q}_S/\dot{Q}_T$ denotes intrapulmonary shunt (blood flow to lung units with $\dot{V}_A/\dot{Q}$ ratios below 0.005), low $\dot{V}_A/\dot{Q}$ denotes perfusion of lung areas with low $\dot{V}_A/\dot{Q}$ ratios ($0.005 < \dot{V}_A/\dot{Q} < 0.1$), $\dot{V}_D/\dot{V}_T$ dead space

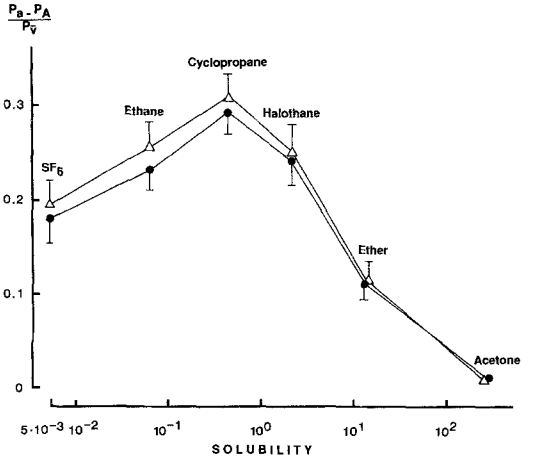

Fig. 3. Arterial-alveolar inert gas pressure differences normalized for the mixed venous partial pressure (*y-axis*) plotted against the inert gas solubilities (*x-axis*) in the control period (*open triangles*) and during fat infusion (*closed circles*). Data are expressed as mean ± SEM. Note that the two curves are virtually identical

Discussion

In the present study we investigated the pulmonary hemodynamic and gas exchange effects of an intravenous fat emulsion containing 50% medium chain triglycerides in patients with the sepsis syndrome. Furthermore, we sought to determine whether any such effects could be attributed to the fat emulsion acting as a substrate for increased prostaglandin production.

The major finding of this study is that in our patients the i.v. fat administration did not induce any alterations in pulmonary hemodynamics nor in gas exchange. In particular, there was no influence on the distributions of ventilation and perfusion. This result was underscored by the lack of changes in the normalized arterial-alveolar inert gas partial pressure differences which confirm that there was neither increased intrapulmonary shunt, worsening of ventilation/perfusion mismatch nor increased dead space ventilation. Hence, probably none of the potential mechanisms [4, 9] which could alter arterial oxygenation during intravenous fat use assumed any importance: increased formation of vasodilator prostaglandins (such as prostacyclin) should increase the shunt fraction as demonstrated by infusing prostacyclin in patients with ARDS [19]. In contrast, aggregation of fat particles with pulmonary microembolism [20] should predominantly cause increased ventilation-perfusion mismatch by developing areas of high $\dot{V}_A/\dot{Q}$ ratios and an increased dead space such as shown in experimental fat embolism [21]. At last, an increase in the shunt fraction and/or perfusion of lung regions with low $\dot{V}_A/\dot{Q}$ ratios which are causes of arterial hypoxemia in pulmonary macroembolism [22–24] did not occur either.

The lack of changes in pulmonary hemodynamics and gas exchange contrasts with data from other authors [1, 2] who reported increased mean pulmonary artery pressure and a fall of arterial PO_2 due to increased venous admixture, in particular in patients with septic acute respiratory failure [2]. In these studies the infusion rate of the fat emulsion as well as the patients' baseline physiologic data were similar to those in our study. The rise in plasma triglyceride levels, which in the past has been suggested to be reponsible for the reported hemodynamic and gas exchange response [25, 26], was comparable to the infusion of long chain triglycerides at equivalent infusion rates as well [6, 27]. Therefore, the different composition of the fat emulsion may explain the discrepancy between our study and the previous ones. Although equivalent gram weights of lipids were administered, half of the triglycerides consisted of medium chain triglycerides which are faster oxidized than long chain triglycerides [7] without acting as a precursor for prostaglandin formation [6]. Experimetal data, however, show that the production of prostaglandins may be responsible for the hemodynamic and gas exchange effects induced by intravenous fat application [8, 10]. These effects seem to be dose-dependent, inasmuch a slow fat infusion rate would predominantly induce vasodilator prostaglandin production while a rapid infusion would lead to a predominance of vasoconstrictor prostaglandins and thromboxane A_2 [4]. Such a dose-dependency has recently been shown in a group of patients with septic acute respiratory failure [28]. Although no cause effect relationship could be established between plasma prostaglandin levels and the pulmonary hemodynamic and gas exchange response to slow and fast fat infusion, variations of prostaglandin levels were more pronounced during the fast infusion.

Consequently, reducing the administration of polyunsaturated fatty acids might limit the formation of prostaglandins and, thereby, minimize any prostaglandin-related responses to intravenous fat application. The lack of changes in pulmonary vascular pressures, arterial oxygenation, venous admixture or in the production of vasodilator or vasoconstrictor prostaglandins, as measured by urinary 6-keto-$PGF_{2\alpha}$ and TxB_2 respectively, in our patients is in keeping with this hypothesis. Besides, in previous studies [1–3, 28] the amount of infused long chain triglycerides, or that of polyunsaturated fatty acids potentially acting as precursors of prostaglandins, was at least twice as high as in this study.

In summary, we conclude that in our patients with sepsis syndrome infusing a fat emulsion consisting of 50% medium and long chain triglycerides did not cause any alterations in pulmonary hemodynamics, arterial oxygenation nor in the distributions of ventilation and perfusion. The urinary excretion of 6-keto-prostaglandin $F_{2\alpha}$ and thromboxane B_2 remained unchanged as well. Hence, partly replacing long chain triglycerides by medium chain triglycerides not only offers the advantage of faster oxidation [6, 7] but may also minimize deleterious pulmonary hemodynamic and gas exchange responses because of limited prostaglandin formation. This may be of help to optimize the clinical management of septic patients.

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