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Gas exchange and pulmonary haemodynamic responses to fat emulsions in acute respiratory distress syndrome

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Abstract *Objective*: To investigate the gas exchange and pulmonary haemodynamic responses to two different intravenous fat emulsions in patients with acute respiratory distress syndrome (ARDS).
Design: Prospective, randomized, double-blind, placebo-controlled study.
Setting: Intensive care unit in a university-affiliated hospital.
Patients: 21 patients with ARDS [mean age, 57 ± 3 (SEM) years; Acute Physiology and Chronic Health Evaluation II, 20 ± 3; Murray's score, 2.85 ± 0.12] consecutively admitted.
Interventions: Patients were assigned to three groups ($n = 7$ each): group A (LCT) received long-chain triglycerides (20% LCT), group B (MCT/LCT), medium-chain triglycerides/long-chain triglycerides (20% MCT/LCT: 50/50) and group C placebo (0.9% sodium chloride, NaCl). The infusion was always given at the rate of 2 mg/kg min over a total period of 12 h, with a volume infusion of 500 ml in each group.
Measurements: Data were collected before, immediately after and 12 h after infusion ceased. Pulmonary and systemic haemodynamic and gas exchange variables were measured at each time point. Serum triglyceride cholesterol, and non-esterified fatty acids levels were measured.
Results: During LCT infusion, cardiac output, oxygen consumption and oxygen delivery increased (all $p < 0.05$), whereas pulmonary haemodynamics, arterial oxygen tension, mixed venous partial pressure of oxygen and venous admixture ratio remained essentially unaltered. No changes were observed following MCT/LCT infusion.
Conclusions: The administration of LCT emulsion given at a slow rate did not alter arterial oxygenation because of the beneficial effect of a high cardiac output, hence offsetting the detrimental effect of increased O_2 consumption.

Key words Acute lung injury · Cardiopulmonary interactions · Eicosanoids · Lipid emulsions · Nutritional support · Prostaglandins

Introduction

Intravenous lipid administration induces transient hyperlipemia according to the lipid clearance rate [1] that has the potential to alter pulmonary gas exchange [2]. The association of heparin with lipid infusions clears the serum of triglycerides but does not influence the increments of pulmonary artery pressure nor the decreased arterial oxygen tension (PaO_2) induced by the intravenous administration of fat emulsions [2, 3]. The latter effects are, however, prevented with indomethacin, a prostaglandin inhibitor, hence suggesting that lipid-induced alterations in pulmonary vasomotor tone could be associated with the ex-

cessive release of arachidonic acid-derived mediators [3, 4].

The intravenous fat emulsions used in humans consist, to a great extent, of polyunsaturated fatty acids (linoleic and alpha-linolenic acid), which are precursors of the eicosanoids (prostaglandins, thromboxanes and leukotrienes). The eicosanoids generated from linoleic acid (n-6) and alpha-linolenic acid (n-3) exhibit physiological properties which are quite different, those from n-3 being less biologically active. Effects within the lungs mediated by the eicosanoids include various immunologic, vasomotor tone and inflammatory responses. Since linoleic acid and alpha-linolenic acid compete for the same chain-elongation and desaturation enzyme systems, the eicosanoids produced depend on the availability of precursors [4–9].

The administration of LCT lipid emulsions have been associated with different pulmonary function changes according to the dose, rate and duration of the infusion, and also the underlying pathophysiological status of the patient studied [9–12]. Radermacher et al. [13], in patients with sepsis, and Fiaccadori et al. [14], in patients following valvular heart surgery, did not observe changes in pulmonary haemodynamics nor in gas exchange abnormalities after the administration of an intravenous fat emulsion containing a physical mixture of medium-chain triglycerides and long-chain triglycerides (MCT/LCT: 50/50). MCT/LCT emulsions provide 26% of linoleic acid and 4% of alpha-linolenic acid, while those of LCT provide 55% of linoleic acid and 7% of alpha-linolenic acid.

The current study was undertaken to evaluate, in patients with acute respiratory distress syndrome (ARDS), the pulmonary haemodynamic and gas exchange responses to two intravenous lipid emulsions providing different amounts of prostanoid precursors. We hypothesized that the administration of an emulsion with less amounts of linoleic acid could induce fewer undesirable effects in the lungs of patients with ARDS.

Patients and methods

Patients

Twenty-one consecutive patients with ARDS [19 males; mean ± (SEM) age 57 ± 3 years, range 34 to 74 years] were included in the study, which was approved by the Research Committee on Human Investigations of Hospital General Universitari Vall d'Hebron. All patients and/or their relatives gave written informed consent before patients were included in the study. Gender, age, diagnosis, baseline arterial oxygenation [expressed as PaO_2/FIO_2 (fractional inspired ratio)], lung injury score [evaluating PaO_2/FIO_2 ratio, positive end-expiratory pressure (PEEP) and chest roentgenogram infiltrates at the time of ARDS diagnosis] [15] and outcome are given in Table 1. Inclusion criteria were: chest roentgenogram showing bilateral pulmonary infiltrates; PaO_2/FIO_2 ratio < 200; pulmonary capillary wedge pressure < 18 mmHg [16]; and lung injury score ≥ 2.5. We excluded patients with dyslipemia, diabetes mellitus and hepatic or renal failure, and also patients who had been on anti-inflammatory drugs and under another heparinization different to common prophylaxis the week before or during the study. All of the patients were mechanically ventilated using a volume-cycled ventilator (Puritan Bennett 7200, Carlsbad, Calif., USA). They remained stable haemodynamically during the study without changes in volume perfusion and ventilatory pattern [FIO_2 0.8 ± 0.04, range 0.55–1.0; PEEP 4.9 ± 0.8 cmH_2O, range 2–10 cmH_2O). The patients were sedated with morphine and midazolam and muscle relaxants were not used. No changes in vasoactive drugs were made during the trial. The study was begun within the first 48 h of ARDS onset. All the patients underwent monitoring for electrocardiography (ECG), heart rate (HR) and arterial O_2 saturation through a pulse oximeter (Nellcor N-180, Pleasanton, Calif., USA).

Table 1 Clinical characteristics of the patients (*S* survivor, *NS* nonsurvivor, *LCT* long chain triglyceride emulsion, *MCT/LCT* medium chain triglyceride and LCT admixture emulsion)

Diagnosis	Gender	Age (years)	PaO_2/FIO_2 ratio	Score [15]	Outcome
Group A: LCT					
1. Aspiration	M	51	72	3.3	S
2. Aspiration	M	48	72	3.3	NS
3. Sepsis	M	74	101	2.7	NS
4. Multiple transfusions	M	46	132	2.7	S
5. Pneumonia	F	68	64	3	NS
6. Aspiration	F	65	107	2.7	NS
7. Aspiration	M	44	127	2.5	S
Group B: MCT/LCT					
8. Pancreatitis	M	67	159	2.7	NS
9. Peritonitis	M	74	183	3	NS
10. Multiple transfusions	M	65	199	2.7	S
11. Pneumonia	M	66	89	3.3	NS
12. Fumes inhalation	M	53	77	3.3	NS
13. Peritonitis	M	69	75	3	NS
14. Aspiration	M	43	152	2.7	S
Group C: control					
15. Aspiration	M	64	137	2.8	S
16. Aspiration	M	66	69	2.7	NS
17. Aspiration	M	34	141	3	NS
18. Peritonitis	M	56	76	3	NS
19. Aspiration	M	51	147	3	S
20. Multiple trauma	M	50	135	2.7	S
21. Lung contusion	M	35	178	2.5	S

Measurements

A central venous catheter was inserted to administer the emulsions. Tidal volume and respiratory rate were monitored using the patient data from the information collected, integrated and stored by the ventilator. Cardiac output (CO) was measured in triplicate by the thermodilution technique (with 10 ml of 5% dextrose in water at ice-bath temperature injection) (Abbott Oximetrix SO_2/CO computer, North Chicago, Ill., USA). Systemic and pulmonary vascular pressures were measured by transducers zeroed to atmospheric pressure at the level of mid-anteroposterior thoracic diam-

eter and calibrated electronically. Systemic (SVR) and pulmonary vascular resistances (PVR) were also calculated using standard equations. Blood samples were collected anaerobically through catheters inserted into radial and pulmonary arteries. Systemic arterial and pulmonary arterial (mixed venous) partial pressures of oxygen and carbon dioxide and pH were analyzed using standard electrodes (NOVA Biomedical, Waltham, Mass., USA). Haemoglobin concentration was measured with a MAXM oximeter (Isaza, Madrid, Spain). Venous admixture ratio ($\dot{Q}_{va}/\dot{Q}_t$), O_2 consumption ($\dot{V}O_2$), O_2 delivery (DO_2) and O_2 extraction ratio (ER), were calculated using standard formulae [$\dot{V}O_2 = CO \times (CaO_2 - C\bar{v}O_2)$; $DO_2 = CO \times CaO_2$; and $ER = (CaO_2 - C\bar{v}O_2)/CaO_2)$]. Serum triglyceride, cholesterol and non-esterified fatty acids levels were measured by the enzymatic method.

Study design

During the first 48 h of ARDS onset and before artificial nutrition was initiated, the patients were randomly assigned to three different groups of treatments according to the emulsion administered ($n = 7$ each). Group A (LCT) received a long-chain triglyceride emulsion (20% LCT) (Intralipid, Pharmacia, Sant Cugat del Vallés, Spain); group B (MCT/LCT), a mixture of medium-chain triglyceride and long-chain triglyceride emulsion (20% MCT and LCT, 50/50) (Lipofundin, B. Braun Medical, Barcelona, Spain); and group C, 500 ml placebo (0.9% sodium chloride, NaCl). Each emulsion was administered for a period of 12 h, at a continuous rate of 2 mg/kg min, with a total infusion volume of 500 ml. Measurements were done at baseline (before the infusion), immediately at the end of the infusion, and 12 h after the infusion was stopped. All sets of measurements consisted of the following steps in sequence: (a) ventilatory and ECG recordings, (b) arterial and mixed venous blood samplings, and (c) systemic and pulmonary haemodynamic recordings.

Data analysis

All parameters were tested using a BMDP Statistical Software package (Los Angeles, Calif., USA). Data are expressed as mean ± SEM. The differences in time of the different parameters studied, depending on the type of the emulsion, were assessed by an analysis of variance (ANOVA) for repeated measures. When we detected statistically significant differences, we analysed them at each time with the Wilcoxon test. This analysis was done separately for each type of emulsion. Significance was set at a p value ≤ 0.05.

Results

The distribution of age, severity score, lung injury score and outcome was similar among groups. Except for CO, HR and DO_2 no significant differences were observed at baseline. During fat infusion in patients receiving LCT fat emulsion, both trygliceride and non-esterified fatty acid levels increased (triglycerides: from 239 ± 105 to 390 ± 110 mg/dl, $p < 0.005$; non-esterified fatty acids: from 0.41 ± 0.14 to 0.78 ± 0.63 mmol/l, $p < 0.05$), but returned to baseline values at the postinfusion period. Changes in the MCT/LCT patients were

Table 2 Haemodynamic and ventilatory patterns in the three groups *A,B,C* of ARDS patients, before, at the end and 12 h after the lipid infusion. Values are mean ± SEM (V_T tidal volume, *f* respiratory rate, *HR* heart rate, *CO* cardiac output, *PS* systemic arterial pressure, *SVR* systemic vascular resistance, *RAP* right atrial pressure, *PAP* pulmonary arterial pressure, *Pw* pulmonary wedge pressure, *PVR* pulmonary vascular resistance)

	Before	End	After
Temp. (°C)			
A	37.3 ± 0.3	38.3 ± 0.2***	37.9 ± 0.3
B	37.9 ± 0.3	37.9 ± 0.3	37.3 ± 0.8
C	37.6 ± 0.3	37.4 ± 0.3	37.4 ± 0.2
V_T (ml)			
A	671 ± 24	669 ± 23	670 ± 23
B	657 ± 23	676 ± 23	675 ± 21
C	679 ± 26	679 ± 26	692 ± 27
f (min^{-1})			
A	15 ± 2	16 ± 2	16 ± 2
B	18 ± 2	18 ± 3	18 ± 2
C	17 ± 2	16 ± 2	18 ± 2
HR (min^{-1})			
A	87 ± 4	96 ± 6	90 ± 5
B	108 ± 9	113 ± 9***	101 ± 9
C	110 ± 5	118 ± 12***	123 ± 10***
CO (l/min)			
A	5.6 ± 0.5	6.3 ± 0.5*	5.9 ± 0.7
B	7.2 ± 0.9	7.9 ± 0.8	8.1 ± 0.9
C	7.4 ± 0.6	7.7 ± 0.6	7.7 ± 0.8
PS (mm Hg)			
A	79 ± 7	81 ± 8	78 ± 6
B	76 ± 4	76 ± 2	84 ± 4
C	83 ± 2	81 ± 4	80 ± 3
SVR (dyn. s/cm^{-5})			
A	988 ± 79	912 ± 89	981 ± 51
B	696 ± 126	602 ± 46	524 ± 34
C	816 ± 54	799 ± 37	709 ± 73
RAP (mm Hg)			
A	11 ± 1	9 ± 1	10 ± 1
B	10 ± 2	10 ± 2	9 ± 1
C	11 ± 1	10 ± 2	10 ± 2
PAP (mm Hg)			
A	31 ± 7	26 ± 2	26 ± 2
B	26 ± 2	26 ± 2	25 ± 3
C	25 ± 3	26 ± 3	25 ± 2
Pw (mm Hg)			
A	11 ± 1	11 ± 1	12 ± 1
B	11 ± 1	10 ± 1	12 ± 1
C	10 ± 2	9 ± 2	9 ± 1
PVR (dyn. s/cm^{-5})			
A	311 ± 57	200 ± 40	203 ± 36
B	165 ± 52	150 ± 28	119 ± 26
C	162 ± 33	183 ± 29	181 ± 21

* $p = 0.01$; *** $p = 0.05$

Table 3 Gas exchange responses in the three groups *A,B,C* of ARDS patients, before, at the end and 12 h after the lipid infusion. Values are mean ± SEM ($A\text{-}aPO_2$ alveolar-arterial PO_2 difference, $P\bar{v}O_2$ mixed venous PO_2, $\dot{Q}_{va}/\dot{Q}_t$ venous admixture ratio, $\dot{V}O_2$ O_2 consumption, DO_2 O_2 delivery, *ER* O_2 extraction ratio)

	Before	End	After
pH			
A	7.45 ± 0.02	7.43 ± 0.03	7.43 ± 0.03
B	7.42 ± 0.03	7.41 ± 0.03	7.44 ± 0.02
C	7.44 ± 0.03	7.43 ± 0.02	7.43 ± 0.04
PaO_2 (mm Hg)			
A	87 ± 8	75 ± 6	81 ± 12
B	90 ± 6	90 ± 1	86 ± 5
C	96 ± 8	89 ± 9	95 ± 7
$PaCO_2$ (mm Hg)			
A	41 ± 3	42 ± 3	42 ± 3
B	42 ± 3	41 ± 3	41 ± 3
C	39 ± 2	38 ± 2	41 ± 4
$A\text{-}aPO_2$ (mm Hg)			
A	514 ± 32	508 ± 43	499 ± 45
B	392 ± 65	373 ± 66	392 ± 87
C	426 ± 51	413 ± 62	448 ± 39
$P\bar{v}O_2$ (mm Hg)			
A	38 ± 2	35 ± 1***	35 ± 2
B	39 ± 1	37 ± 2***	39 ± 1
C	38 ± 1	38 ± 1	39 ± 2
$\dot{Q}_{va}/\dot{Q}_t$ (%)			
A	46 ± 4	47 ± 4	49 ± 7
B	40 ± 6	41 ± 6	41 ± 7
C	43 ± 7	51 ± 11	47 ± 5
$\dot{V}O_2$ (ml/min)			
A	232 ± 26	275 ± 28**	243 ± 17
B	299 ± 30	339 ± 34	330 ± 20
C	274 ± 16	285 ± 18	264 ± 22
DO_2 (ml/min)			
A	839 ± 89	933 ± 95**	826 ± 70
B	1099 ± 135	1150 ± 98	1254 ± 103
C	1076 ± 70	1088 ± 75	1078 ± 97
ER (%)			
A	28 ± 2	30 ± 1	30 ± 1
B	26 ± 2	29 ± 4	25 ± 2
C	26 ± 1	27 ± 1	25 ± 2

** $p = 0.03$; *** $p = 0.05$

similar (tryglicerides rose from 151 ± 77 to 485 ± 332 mg/dl, $p < 0.005$; non-esterified fatty acids from 0.42 ± 0.21 to 1.10 ± 0.55 mmol/l, $p < 0.05$). No changes in cholesterol levels were observed in any of the groups. In the control group, there were no changes in either tryglicerides or non-esterified fatty acids.

During lipid infusion (Table 2), temperature increased transiently in group A (LCT) only ($p = 0.05$); HR increased transiently in group B (MCT/LCT) during infusion, while in group C (control) it increased even after the infusion was stopped (each $p = 0.05$). Likewise, patients in group A (LCT) showed a transient increase in CO (by 13%) ($p = 0.01$) and also a trend to decreased (PVR) (by 36%, $p = 0.06$), findings not observed in the other two groups. As shown in Table 3, compared to the other two regimens, in group A (LCT) there was a transient increase in both $\dot{V}O_2$ (by 19%) and DO_2 (by 11%) during the infusion (each $p = 0.03$) while mixed venous PO_2 ($P\bar{v}O_2$) decreased (by 2.4 mmHg) ($p = 0.05$) and ER remained unchanged; by contrast, no changes in the other gas exchange indices (PaO_2, arterial carbon dioxide tension and $\dot{Q}_{va}/\dot{Q}_t$), including arterial pH, were observed in this subset of patients. In group B (MCT/LCT) there were no noticeable changes except for a mild reduction in $P\bar{v}O_2$ (by 1.7 mmHg; $p = 0.05$) during the infusion, possibly without pathophysiological significance. No significant changes in the total amount of fluid administered were observed among groups.

Discussion

The most novel finding of our study is that, in this population of ARDS patients, the administration of both fat emulsions at the rate of 2 mg/kg min did not essentially alter arterial oxygenation. Compared to group B (MCT/LCT), patients treated with higher amounts of prostanoid precursors [group A (LCT)] showed transient increases in body temperature, CO, $\dot{V}O_2$ and DO_2, along with a mild reduction in $P\bar{v}O_2$. It is conceivable that PaO_2 during LCT remained unaltered because the beneficial effect of a high CO on PaO_2, hence offsetting the detrimental effect of increased $\dot{V}O_2$ on PaO_2 through decreased $P\bar{v}O_2$, played a pivotal role in attenuating the fall in PaO_2 [17, 18]. Furthermore, the increase in CO was sufficiently effective not only to counterbalance the associated increments of $\dot{V}O_2$ but also to increase slightly the delivery of O_2 to peripheral tissues. However, because of the small number of patients included in each therapeutic regimen, we cannot ignore the possibility of a Type II error.

Lipid emulsion-induced pulmonary gas exchange disturbances can vary due to several factors, namely the different amounts of prostanoid precursors administered [4, 8, 10, 13, 14], the rate and duration of the lipid perfusion, and/or the pre-existing pathophysiological status of the lung [9, 12].

The cardiopulmonary findings induced by the administration of intravenous lipid emulsions containing large amounts of linoleic acid, in patients with acute lung injury, have shown conflicting results [9–12]. Table 4 shows the main clinical pulmonary results from human trials using lipid emulsions [9–14]. Thus, the administration of 20% LCT (500 ml over 10 h) disturbed gas exchange and increased pulmonary artery pressure in critically ill (septic and non-septic) patients [10]. In patients with ARDS, the infusion of 20% LCT (500 ml over 8 h) caused a deterioration in arterial oxygenation

Table 4 Main clinical pulmonary results in human studies according to the class of infusions and baseline illness (*COPD* chronic obstructive pulmonary disease, *PAP* pulmonary artery pressure, $\dot{Q}_s\dot{Q}_t$ venous admixture ratio)

Author	Emulsion	Infusion	Patients	Results
Venus et al. [10]	20% LCT	100 g/10 h	Sepsis	↑ PAP and $\dot{Q}_s/\dot{Q}_t$
		100 g/10 h	No sepsis	↑ PAP and $\dot{Q}_s/\dot{Q}_t$
Venus et al. [11]	20% LCT	100 g/8 h	ARDS	↑ PAP, $\dot{Q}_s/\dot{Q}_t$, PVR and ↓ PaO_2/FIO_2
Hwang et al. [12]	10% LCT	50 g/4 h	Healthy	↓ $\dot{Q}_s/\dot{Q}_t$, ↑ PaO_2/FIO_2
		50 g/4 h	ARDS	↑ $\dot{Q}_s/\dot{Q}_t$, ↓ PaO_2/FIO_2
		50 g/4 h	Pneumonia	No changes
		50 g/4 h	COPD	No changes
Mathru et al. [9]	20% LCT	100 g/10 h	ARDS	↑ $\dot{Q}_s/\dot{Q}_t$, = PAP
		100 g/5 h	ARDS	= $\dot{Q}_s/\dot{Q}_t$, ↑ PAP
Radermacher et al. [13]	20% MCT/LCT	50 g/4 h	Sepsis	No changes
Fiaccadori et al. [14]	20% MCT/LCT	3.3 mg/kg · min	Heart surgery	No changes

with increases in the pulmonary vascular variables, more markedly in patients with coexisting sepsis [11]. Intravenous fat infusion (500 ml of 10% LCT over 4 h) altered pulmonary gas exchange in patients with ARDS, whereas it had little effect in patients with infectious pulmonary disease or chronic obstructive pulmonary disease. The same infusion, however, improved overall gas exchange in patients with normal lungs [12]. A slow fat infusion of 20% LCT (500 ml over 10 h) increased intrapulmonary shunt, suggesting increased production of endogenous vasodilators, whereas a fast fat infusion of 20% LCT (500 ml over 5 h) increased the pulmonary vascular tone, thereby indicating increased production of endogenous vasoconstrictors. However, a true cause and effect relationship between plasma levels of prostanoids and the observed pulmonary haemodynamic and gas exchange responses remains elusive [9].

In the group of patients who received MCT/LCT, with lower amounts of prostanoid precursors, neither gas exchange nor pulmonary haemodynamics were altered, a finding akin to previous observations [13, 14]. Although equivalent gram weights of lipids were administered with the MCT/LCT emulsion and with the LCT, in the MCT/LCT preparation half of the triglycerides consist of MCT, which are oxidized faster than LCT without acting as a precursor for prostanoid formation [19].

We previously observed a significant decrease in systemic-pulmonary arterial 6-keto-prostaglandin α (a stable inactive metabolite of the vasodilator prostacyclin) difference in ARDS patients treated with LCT emulsion, a reduction that was possibly due to a tendency of this marker to increase at the pulmonary arterial levels and due also to a trend to decrease at the systemic arterial level [20].

Taken altogether, intravenous lipid emulsions with high concentrations of both linoleic acid and alpha-linolenic acid given at a slow rate can be administered effectively and safely in this population of patients with ARDS. The increased CO shown following the infusion of this class of emulsions is sufficiently efficacious to override the deleterious effect on arterial oxygenation induced by the associated increased O_2 metabolic demands; furthermore, the delivery of O_2 to peripheral tissues is slightly ameliorated.

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