Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury*

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Objective: **To explore the effects of an enteral diet enriched with eicosapentaenoic acid (EPA), gamma-linolenic acid (GLA), and antioxidants on the respiratory profile and outcome of patients with acute lung injury.**

Design: **Single-center, prospective, randomized, controlled, unblinded study.**

Setting: **General intensive care department of a tertiary-care, university-affiliated hospital.**

Patients: **A total of 100 patients with acute lung injury, diagnosed according to the American-European Consensus Conference on ARDS.**

Interventions: **Patients were randomized to receive the standard isonitrogenous, isocaloric enteral diet or the standard diet supplemented with EPA and GLA for 14 days.**

Measurements and Main Results: **Patient demographics, Acute Physiology and Chronic Health Evaluation II score, and type of admission were noted at admission. Compared with baseline oxygenation (EPA + GLA group vs. control group), by days 4 and 7, patients receiving the EPA + GLA diet showed significant improvement in oxygenation (Pao_2/Fio_2, 317.3 ± 99.5 vs. 214.3 ± 56.4 and 296.5 ± 165.3 vs. 236.3 ± 79.8, respectively; $p < .05$). Compliance was significantly higher in the EPA + GLA group observed at day 7 (55.1 ± 46.5 vs. 35.2 ± 20.0 mL/mbar, $p < .05$). No significant difference was found in nutritional variables. Resting energy expenditure was significantly higher in patients in the EPA + GLA group, but their body mass index was also higher ($p < .05$). A significant difference was found in length of ventilation ($p < .04$) in favor of the EPA + GLA group. There was no between-group difference in survival.**

Conclusions: **In patients with acute lung injury, a diet enriched with EPA + GLA may be beneficial for gas exchange, respiratory dynamics, and requirements for mechanical ventilation. (Crit Care Med 2006; 34:1033–1038)**

KEY WORDS: borage oil; fish oil; antioxidants; acute lung injury; enteral feeding; mechanical ventilation

Acute lung injury (ALI) is an abrupt (within 24 hrs) pathologic process in the lungs, often seen as part of a persistent systemic syndrome of inflammation. It is characterized by increased permeability in the lung unexplained by pulmonary capillary hypertension and by hypoxemia resistant to oxygen therapy (Pao_2/Fio_2 of <300 mm Hg), regardless of the positive end-expiratory pressure (PEEP) (1). Bilateral infiltrates are noted on chest radiographs, combined with high levels of albumin in the alveolar fluid (2). The severe form is termed acute respiratory distress syndrome (ARDS). In some cases, the lung is damaged directly by the action of the mechanical ventilator (3), a factor that adds considerably to the mortality risk (3). Therefore, some researchers have recommended a ventilatory strategy to improve survival (4). In addition, recent evidence suggests that nutritional intervention with dietary fish oil containing eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA), which modulate proinflammatory eicosanoid and prostaglandin E1 production, may be beneficial. Rats fed a diet enriched with EPA and GLA showed both reduced lung microvascular protein permeability after endotoxin administration and improved oxygenation (5, 6). In a clinical trial, Gadek et al. (7) noted a decrease in inflammation in patients with ARDS given EPA and GLA compared with controls. The study group also required fewer days of ventilation and had a shorter stay in the intensive care unit (ICU). More recently, Pacht et al. (8) reported that patients with ARDS given EPA- and GLA-enriched enteral nutrition had a decrease in alveolar neutrophil recruitment and inflammatory response, followed by a decrease in interleukin-8 release, in addition to reduced morbidity. However, because patients with ARDS account for only a small proportion of the general ICU population, data on their inflammatory and metabolic responses and on the role of dietary supplements in this patient group remain sparse. Furthermore, none of the studies has so far focused on patients with ALI.

The purpose of the present study was to assess and explore the effects of an enteral diet enriched with EPA, GLA, and antioxidants (EPA + GLA diet) in patients with ALI/ARDS hospitalized in our ICU. Primary outcome measures were oxygenation and respiratory mechanics, and secondary outcomes included length of ventilation, length of stay, and mortality.

MATERIALS AND METHODS

An open, controlled, prospective, randomized design was used. Patients with ALI/ARDS according to the American-European Consensus Conference on ARDS (1) who were treated in the general intensive care department of our center from February 2002 to August 2003 were prospectively included in the study. The study protocol was approved by the local institutional review board and informed consent

***See also p. 1265.**

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to participate in the study was obtained before randomization. Exclusion criteria included patients with head trauma, cerebral hemorrhage, or active bleeding (because fish oil has been reported to increase coagulation disorders), patients receiving an immuno-suppression regimen including >0.25 mg·kg^{-1}·day^{-1} prednisone, HIV-positive patients, and pregnancy.

Patients were randomized to control and EPA + GLA diet groups by a program designed with the use of independent data management and statistical software. The control group received a diet that was a ready-to-feed, high-fat, low-carbohydrate, enteral formula (Pulmocare, Ross Laboratories, Chicago, IL). The study group formula (Oxepa, Ross Laboratories) diet differed from the control group diet only in lipid composition (supplemental GLA and EPA) and in the level of antioxidants (Table 1); the caloric and nitrogenous contents were identical. All participants were started on enteral feeding through a nasogastric, duodenal, or jejunal tube within 24 hrs of ICU admission. The diet feeding in both groups was adjusted to achieve $\geq$50% of the measured resting energy expenditure (REE) $\times$ 1.2 on the first day and 70% REE $\times$ 1.2 from the second day. Enteral feeding was administered continuously, and the daily enteral intake was recorded. Patients received the same enteral formula throughout their stay in the ICU.

Conventional modes of ventilation were used in all cases, including assist control ventilation (pressure mode), pressure support ventilation, and automatic tube compensation (Evita 4, Drager, Lubeck, Germany). The main goals of mechanical ventilation were an oxygen saturation of $>$90%, peak airway pressure of $<$35 cm H_2O, and tidal volume of $<$7 mL/kg. Levels of PEEP and F_{IO_2} were adjusted to achieve these goals. Ventilation settings and decisions regarding readiness for extubation were left to the discretion of physicians who were blinded to the nutritional prescription.

Data Collection

The following data were collected for each patient admitted to the ICU.

Demographic Data. Age, sex, weight, height, body mass index, and diagnostic category for ICU admission (medical, surgical, or trauma) were recorded.

Assessment of Oxygenation and Respiratory Function. Oxygenation was assessed by measuring arterial blood gases (AVL Omni Technology, Graz, Austria) at baseline; after 4, 7, and 14 days; or at discharge from the ICU. The ventilatory setting, including tidal volumes (mL) and PEEP (cm H_2O) values, was recorded simultaneously for calculation of the P_{AO_2}/F_{IO_2} ratio.

Respiratory mechanics were assessed with the mechanics analysis program of the Evita 4 ventilator, which measures static compliance (mL/mbar) and resistance (mbar·L^{-1}·sec^{-1}) with an accuracy to within $\pm$10% according to the manufacturer.

Assessment of Metabolic and Nutritional Variables. Immediately at entry into the study, REE was measured. The volume of oxygen utilization and CO_2 output were measured with a Deltatrac II device (Datex-Ohmeda, Helsinki, Finland) after calibration and a steady state of $\geq$30 mins (9); REE was then calculated by Weir's formula (10). Measurements were not performed in patients with an F_{IO_2} of $>$0.6. The Harris-Benedict equation (11) was used to calculate the predicted energy expenditure according to anthropometric variables. Albumin and prealbumin levels were assessed at baseline and on days 4, 7, and 14 (Hitachi 747 automatic analyzer).

Outcome Measures

Primary outcome measures included change in oxygenation and breathing patterns assessed at days 4, 7, and 14. Secondary outcomes included 1) length of ventilation (LOV), assessed in hours from the time of intubation to the time of liberation from the ventilator (short-term ventilation was the duration of ventilation required below the median ventilation period observed in the total group, and long-term ventilation was the ventilation period above the median ventilation period); 2) length of ICU stay (LOS); 3) length of hospital stay; and 4) in-hospital mortality.

Statistical Analysis

Data are presented as mean values, standard deviations, modes, and median values, as appropriate. All statistical analyses were performed with SPSS 11.0 software (SPSS, Chicago, IL) for Windows (12). Differences between study and control groups were calculated from baseline to day 14.

Patient demographic data and baseline values were compared across the two groups with Student's *t*-tests or one-way analysis of variance for all continuous variables. For multiple comparisons, one-way analysis of variance or repeated-measures analysis of variance was used. All *p* values were two-sided; significance was assigned at a threshold alpha of .05. Analysis of variance for repeated measures was used to compare LOV and length of stay. Survival was evaluated with the Kaplan-Meier curve.

Table 1. Composition of the two formulas

Nutrient	Control	EPA + GLA
Protein:		
% of total calories	16.7	16.7
g/L	62.6	62.5
Source	87% sodium caseinate	87% sodium caseinate
Carbohydrate:	13% calcium caseinate	13% calcium caseinate
% of total calories	28.1	28.1
g/L	105.7	105.5
Source	46% maltodextrin	45% maltodextrin
Lipids:	54% sucrose	55% sucrose
% of total calories	55.2	55.2
g/L	92.1	93.7
Source	96.8% corn oil, 3.2% soy lecithin	31.8% canola oil, 25% MCT, 20% fish oil, 3.2% soy lecithin
Vitamins:		
Vitamin E, IU/L	47.6	317
Vitamin C, mg/L	317	844
β-carotene, mg/L	—	5.0
Taurine, mg/L	—	316
L-carnitine, mg/L	—	181
Caloric density, kcal/mL	1.5	1.5
Osmolality, mOsm·kg^{-1}·H_2O^{-1}	465	493

EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; MTC, medium chain triglycerides.

RESULTS

The final analysis was conducted in 95 of the 100 patients enrolled; reasons for exclusion were introduction of steroid therapy after randomization (n = 2) and severe diarrhea (n = 3). Of the remainder, 49 patients received the control formula, and 46 received the EPA + GLA formula. The demographic and baseline data of the two groups are shown in Table 2. There were no significant differences between the two groups regarding age, sex, diagnostic category for ICU admission, and Acute Physiology and Chronic Health Evaluation (APACHE) II score. However, the body mass index was significantly higher in the EPA + GLA group, and this was reflected in a significantly higher REE. Sixty percent of the patients

were men and 40% women. Only 14% were <40 yrs old, and 58% were >60 yrs old. A total of 35 patients had a medical disease: a surgical pathology in 52% (surgery was performed before admission to the ICU) and multiple trauma in 13%. The EPA + GLA diet group were entered into the study within a mean of 7.22 days of hospital admission (range, 1–29 days) compared with 6.2 days (range, 1–33 days) in the control group (p = not significant). All patients included in the study were fed successfully for ≥14 days through the gastric, duodenal, or jejunal route, and none was dropped because of formula-related safety concerns. Mean time from study entry to achievement of 75% of the REE × 1.2 was 1.91 days for the control group and 2.27 days for the study group (p = not significant). All patients received enteral nutrition for ≥14 days at a rate not exceeding REE × 1.25.

Outcome Measures

Primary Outcome Measures: Oxygenation and Respiratory Mechanics. Oxygenation, shown in Table 3, was significantly higher in the EPA + GLA group on day 4 (Pao_2/Fio_2, 317.3 ± 99.5 vs. 214.3 ± 56.4; $p < .05$) and on day 7 (Pao_2/Fio_2, 296.5 ± 165.3 vs. 236.3 ± 79.8; $p < .05$), but this advantage was lost by day 14 or at discharge. Tidal volumes and PEEP values used during the trial were not significantly different between groups. In the control group, tidal volumes and PEEP values were 517 ± 174 mL and 6.8 ± 3.8 cm H_2O at day 1, 523 ± 168 mL and 6.8 ± 2.2 cm H_2O at day 4, and 535 ± 142 mL and 8.1 ± 3.2 cm H_2O at day 7. In the study group, tidal volumes and PEEP values were 518 ± 214 mL and 7.0 ± 2.6 cm H_2O at day 1, 560 ± 121 mL and 6.8 ± 2.5 cm H_2O at day 4, and 560 ± 121 mL and 7.5 ± 2.5 cm H_2O at day 7. Table 3 describes the number of patients remaining in the study. Patients receiving the EPA + GLA diet showed an improvement in static compliance from day 1 through day 7 (50.1 ± 37.5 to 55.1 ± 31.8 mL/mbar), whereas a decrease was seen in the control group (44.1 ± 26.1 to 35.2 ± 20.0 mL/mbar) ($p < .05$). The day 7 values were significantly higher in the EPA + GLA group. Resistance decreased in the EPA + GLA group, although the change was slight (from 23.1 ± 18.3 to 20.14 ± 6.3 $mbar \cdot L^{-1} \cdot sec^{-1}$). Comparison with the change in the control group (from 22.5 ± 17.2 to 30.9 ± 33.2 $mbar \cdot L^{-1} \cdot sec^{-1}$) yielded a significant difference ($p < .05$).

Secondary Outcome Measures. Median LOV for the whole group was 9 days and median LOS was 11 days. Patients in the EPA + GLA group had a significantly shorter LOV expressed in hours free from ventilation (40 patients were still ventilated in the control group and only 34 in the study group). LOS did not reach significance. Length of hospital stay was similar in the two groups (Tables 4 and 5). Overall survival (Kaplan-Meier curve, Fig. 1) was similar in the two groups. In the EPA + GLA group, 26 out of 46 were alive at 2 wks (namely, 37% mortality), whereas in the control group, 32 out of 49 patients were alive (35% mortality). Survival was followed for 90 days (shown using a Kaplan-Meier curve in Fig. 1) and showed a relatively high hospital mortality rate. When survivors and nonsurvivors were compared in terms of LOV and length of stay, according to their group, the following results were found (Table 4): after 14 days of enteral feeding administration, a significant difference (chi-square = 10.97, $p < .01$) was found in the survival of the study group (three patients did not survive in this group com-

Table 2. Baseline patient characteristics

	Control Diet (n = 49)		EPA + GLA Diet (n = 46)		
	Mean	SD	Mean	SD	p
Age, yrs	62.3	17.2	57.0	18.7	NS
Diagnostic category for ICU admission, medical/surgical trauma, n	15/34		18/28		NS
APACHE II score	22.6	6.9	22.6	6.7	NS
Pao_2/Fio_2 ratio	231	59	207	64	NS
Compliance, mL/mbar	44.1	26.1	50.9	37.5	NS
BMI, kg/m^2	26.5	5.4	28.9	6.2	.05
REE, kcal/day	1850.5	334.2	2132.4	625.7	.01
Harris-Benedict, kcal/day	1471.1	238.4	1569.1	293.9	NS

EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; NS, nonsignificant; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; REE, resting energy expenditure.

Table 3. Gas exchange variations expressed as Pao_2/Fio_2 ratio in the eicosapentaenoic acid + gamma-linolenic acid (EPA + GLA) and control groups

	Control Diet			EPA + GLA Diet			
	Mean	SD	n	Mean	SD	n	p Value
Baseline	230.5	58.7	49	207.7	64.3	46	NS
Day 4	214.3	56.4	42	317.3	99.5	41	.05
Day 7	236.3	79.8	33	296.5	165.3	34	.05
Discharge	242.7	104.3	34	253.9	111.9	28	NS
Day 14	305.2	126.9	15	274.8	81.2	14	NS

n, Number of patients remaining in the study; NS, not significant. Significant difference was reached at days 4 and 7.

Table 4. Outcome variables in the eicosapentaenoic acid + gamma-linolenic acid (EPA + GLA) and control groups

Mean ± SD (n)	Day 1 (44/48)	Day 4 (44/47)	Day 7 (34/40)	Day 14 (24/35)
LOV				
EPA + GLA	24.0 ± 0	89.6 ± 17.6	160.4 ± 15.2[a]	279.2 ± 58.2
Control	23.6 ± 3.0	90.9 ± 14.7	166.8 ± 5..2	293.2 ± 53.9
LOS				
EPA + GLA	24.0 ± 0	90.8 ± 16.0	163.0 ± 11.6	290.8 ± 54.8
Control	23.6 ± 2.4	93.6 ± 11.4	165.7 ± 8.8	299.0 ± 51.5

Results are expressed as mean ± SD hours of ventilation (LOV) and length of stay (LOS); n is the number of patients in the study at the day of analysis in the EPA + GLA group or the control group, respectively.

[a]Significant difference ($p < .03$) was reached at day 7 in the length of ventilation in favor of the EPA + GLA group.

Table 5. Length of ventilation (LOV) and intensive care unit length of stay (LOS) in hours are compared in the total group of 28-day survivors and nonsurvivors receiving control diet or eicosapentaenoic acid + gamma-linolenic acid (EPA + GLA) diet

	Control	EPA + GLA	*p* Value
Survivors, n	21	33	.007
LOV	421.9 ± 359.2	314.1 ± 310.9	NS
LOS	441.9 ± 341.9	356.3 ± 323.9	NS
Nonsurvivors, n	28	13	.004
LOV	302.8 ± 220.3	233.3 ± 129.9	NS
LOS	326.2 ± 227.7	249.4 ± 130.8	NS

NS, not significant.
Results are expressed as mean ± SD hours for LOV and LOS.

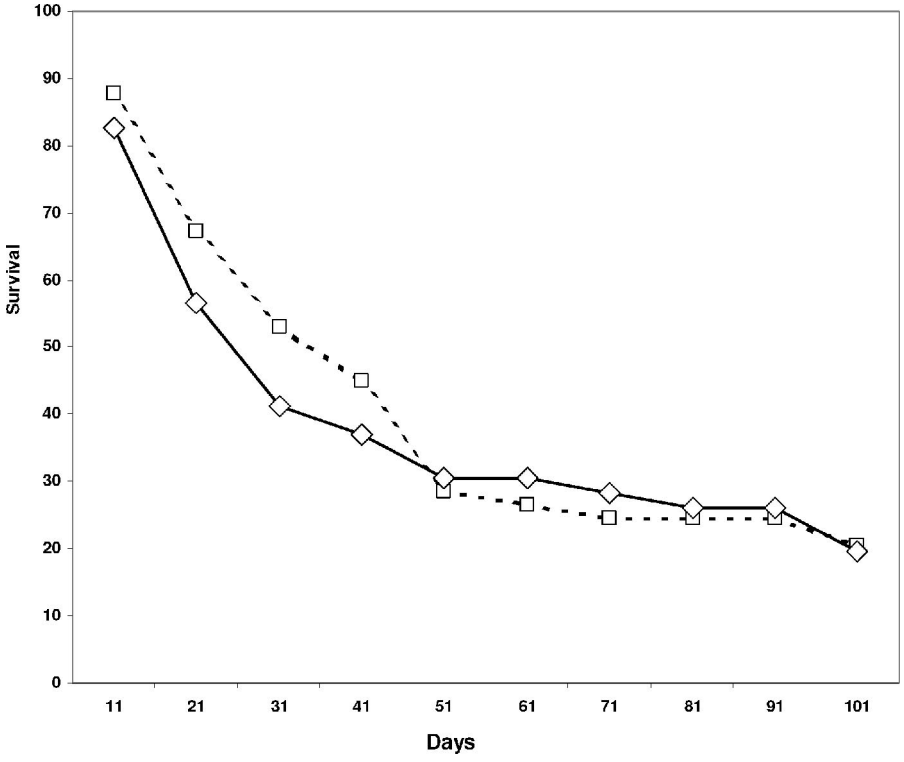

Figure 1. Kaplan-Meier curve of survival, comparing the eicosapentaenoic acid + gamma-linolenic acid diet group (*squares*) with the control group (*diamonds*). No significant difference was found.

pared with 15 in the control group). When the total group of survivors and nonsurvivors were compared in terms of LOV and LOS (Table 5), a trend in favor of the EPA + GLA diet was observed, but no significant difference was achieved due to large SD values. The same trend was observed in survivors and nonsurvivors.

Table 6 shows values of the nutritional variables (weight variations, plasma albumin, and prealbumin) on days 1 and 7. No significant differences were observed.

Metabolic response was assessed by indirect calorimetry. REE was significantly elevated in the study group compared with the controls, as the study group had a significantly higher body mass index ($p < .05$) at baseline (Table 2) and, therefore, a higher total REE. However, when related to weight, the REE in the two groups was similar.

DISCUSSION

This open, prospective, randomized, controlled, single-center study shows the advantages of a diet enriched in fish and borage oil on oxygenation (days 4 and 7), pulmonary static compliance, and resistance in ventilated patients with ALI. The enriched diet was also associated with a small but significantly shorter LOV and no benefit in LOS. In the survivor group, the study patients required less ventilatory support (13.1 ± 12.9 days) in comparison with the control group (17.6 ± 15.0 days, p = not significant). The same trend was observed when considering LOS. Similar results were reported by Gadek et al. (7) in 98 patients with ARDS caused by sepsis/pneumonia, trauma, or aspiration injury, in whom the Pao_2/Fio_2 ratio significantly improved from baseline to days 4 and 7 after enteral feeding with an EPA- and GLA-enriched diet. Their study patients also required less ventilatory support (11 days vs. 16.3 days in the control group, $p < .02$) and had shorter ICU stay (12.8 days vs. 17.5 days in the control group).

In the present series, the two groups were very similar in terms of disease pathogenesis and severity (APACHE II) and in techniques of ventilation with comparable tidal volumes and PEEP values. Although this was not a blinded study, the investigator who compared the outcome variables, who was not the prescription provider, was the only one who knew the exact patient allocation. There were also no between-group differences in severity of ALI by Pao_2/Fio_2 and ventilatory setting. Although the study patients had a significantly higher body mass index ($p < .05$) and, therefore, a significantly higher REE, this difference disappeared after adjustment of enteral feeding to the measured energy expenditure. We may conclude that the better outcome in the EPA + GLA group could be attributable to the composition of the diet, inducing by the action of EPA and GLA on macrophages a decrease in the synthesis of interleukin-8 and leukotriene B4 and thereby reducing the inflammatory process in the lung and improving lung mechanics and oxygenation.

Role of Fat in ALI. Fifteen years ago, Skeie et al. (13) pointed out that intravenous fat emulsions, mainly rapidly administered long-chain triglycerides, were associated with a decrease in prostaglandin production, leading to a decrease in Pao_2 and a ventilation/perfusion inequality. The authors postulated that because the deleterious effects of long-chain triglycerides are blocked by indomethacin, a cyclooxygenase inhibitor, prostaglandin E_2 and prostacyclin might serve as mediators for improving oxygenation. Accordingly, the administration of GLA and EPA may reduce the production of thromboxane and increase the production of prostaglandin E_2 and prostacyclin (14). Suchner et al. (15) demonstrated that prostacyclin and thromboxane A2 influence the vasomotor tone in the pulmonary and systemic circu-

Table 6. Nutritional intake and nutritional assessment

	Control Diet		EPA + GLA Diet		
	Day 1	Day 7	Day 1	Day 7	*p*
Nutritional intake, kcal/day	1055 ± 378	1420 ± 437	1053 ± 351	1624 ± 512	NS
BMI	26.5 ± 5.4		28.9 ± 6.2		.05
Albumin, g/dL	1.96 ± 0.42	2.02 ± 0.62	2.07 ± .51	2.13 ± 0.61	NS
Prealbumin, g/dL	9.76 ± 4.0	11.52 ± 5.20	9.97 ± 5.41	12.79 ± 7.56	NS

EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; NS, not significant; BMI, body mass index. Data provided as mean ± SD, unless otherwise noted.

lations. The adverse effect of linoleic acid was demonstrated in an animal model. Short-term enteral feeding with an EPA + GLA–enriched diet rapidly modulated the fatty acid composition of alveolar macrophage phospholipids and promoted a shift toward the formation of less inflammatory eicosanoids by stimulated macrophages (16, 17).

In our study, the improved lung function in the EPA + GLA group was supported by a significant increase in oxygenation and also by the increase in compliance and decrease in resistance. LOV was decreased at day 7 when compared with controls. However, ICU mortality was relatively high and hospital survival was low (Fig. 1) in both populations, decreasing the number of studied patients and influencing the length of stay. This hospital mortality could be explained by the lack of intermediate care facilities in our hospital and the difficulties encountered by general wards in treating patients after their intensive care stay.

Role of the Lung Injury in Lipid Effects. Suchner et al. (18) compared rapid (6 hrs) and slow (24 hrs) infusion of long-chain triglycerides in septic and ARDS patients. They found that in the septic patients, prostanoid formation was unaffected, even with rapid infusion, but in the ARDS patients, the increased availability of linoleic acid enhanced prostanoid formation. Thromboxane A2 formation was similarly affected by the presence of severe pulmonary organ failure: the higher the lung injury score, the more negative the transpulmonary prostanoid balance. With the transition from severe sepsis to ARDS, the injured lung changes from a prostanoid-producing to a prostanoid-consuming organ. Therefore, the same administration of lipids may be helpful or harmful, according to the condition of the lung.

Ours is one of the first studies of patients with ALI. The American-European Consensus Conference (1) defined ARDS as an acute-onset respiratory failure, with a Pao_2/Fio_2 of <200 mm Hg, irrespective of the PEEP level, and bilateral infiltrates on chest radiographs. ALI was defined as a less severe form of ARDS (Pao_2/Fio_2 of <300 mm Hg). The investigators speculated that the majority of patients with a Pao_2/Fio_2 of <250 mm Hg would eventually fulfill the criteria for ARDS (11). However, this issue remains controversial, with some authors reporting that only 2.3% of their ALI patients developed ARDS (19) and others noting a >67% rate of progression to ARDS (20).

Role of Nutritional Status on Morbidity and Mortality. Nutritional status was assessed by weight variations and plasma concentrations of albumin and prealbumin. No significant difference was observed between the two groups at any of the time points, underlining the difficulty of nutritional assessment in critically ill patients. No correlation was found between the nutritional variables and changes in pulmonary function or morbidity.

A significant increase in REE was observed in the experimental diet group (2132.5 ± 625.7 vs. 1850.5 ± 334.2 kcal/day, $p < .01$), but it was related to their higher initial body mass index (28.9 ± 6.2 vs. 26.5 ± 5.3 kg/m^2, $p < .05$), as demonstrated also in many other conditions. The volume of oxygen utilization and CO_2 output were increased in the same proportion.

We conclude that the effects of EPA and GLA in ALI may be understood by the modulation of arachidonic acid metabolism, which enhances the production of more anti-inflammatory eicosanoids. These changes may interfere with the alveolar membrane and neutrophil stimulation of mediators and with prostaglandin synthesis. Our study demonstrates that this EPA + GLA diet improves oxygenation and lung dynamics, and also morbidity related to the lung condition, decreasing the LOV in the ICU.

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