The Effect of Parenteral Fish Oil on Leukocyte Membrane Fatty Acid Composition and Leukotriene-Synthesizing Capacity in Patients With Postoperative Trauma

Bart J. Morlion, Elisabeth Torwesten, Henri Lessire, Gerlinde Sturm, Brigitta M. Peskar, Peter Fürst, and Christoph Puchstein

The incorporation of ω-3 and ω-6 fatty acids (FAs) into leukocyte membranes and the leukotriene (LT)B_4-, LTB_5 -, LTC_4-, and LTC_5-synthesizing capacity in stimulated leukocytes were measured following parenteral ω-3 FA nutrition in 20 postoperative patients. Total parenteral nutrition (TPN) over 5 days postoperatively was isonitrogenous (0.24 g $N \cdot kg^{-1} \cdot d^{-1}$) and isoenergetic (92 kJ/22 kcal $\cdot kg^{-1} \cdot d^{-1}$), containing 0.15 g fish oil and 0.85 g soybean oil per $kg^{-1} \cdot d^{-1}$ (FO) or 1.0 g soybean oil $\cdot kg^{-1} \cdot d^{-1}$ (SO). Following 5 days' FO administration, the content of eicosapentaenoic acid (EPA) was increased 2.5-fold, LTB_5 1.5-fold, and LTC_5 sevenfold. With SO nutrition, EPA and LTB_5 generation remained unaltered, whereas LTC_5 doubled. The production of LTB_4 and LTC_4 was not affected in any of the groups. We conclude that a 5-day parenteral fish oil supplementation has an immunomodulatory effect on lipid-mediator generation in human leukocytes in postoperative trauma.

THE CURRENT INTEREST in diets enriched with ω-3 fatty acids (FAs), eicosapentaenoic acid ([EPA] 20:5n-3), and docosahexaenoic acid ([DHA] 22:6n-3) has its origin in the epidemiological observation that Greenland eskimos have a lower incidence of atherosclerosis and age-adjusted mortality compared with the general Danish population.[1] The major advantages of EPA- and DHA-acquired metabolites relate to their postulated reduced proinflammatory effects. Important metabolites of ω-3 and ω-6 FAs are the leukotrienes (LTs), known as potent inflammatory mediators. LTB_4, derived from arachidonic acid (AA), enhances chemotaxis, whereas LTC_4, also a product of AA, is a potent constrictor of vascular and bronchial smooth muscle. LTB_5 and LTC_5 are metabolic products of EPA. In contrast to LTB_4 and LTC_4, these lipid mediators exert less metabolic activity. Nevertheless, all LTs are known to play an important role as mediators in sepsis, shock, trauma, and hypermetabolic states.[2,3] LTC_4 especially plays a pivotal role in the development of respiratory dysfunction. Accordingly, a protective effect of ω-3 FAs in the development of cardiovascular[4] and inflammatory[5,6] diseases has been reported. Preliminary observations suggest a potential role for fish oils in the treatment of atopic dermatitis,[7] psoriasis,[8] and cystic fibrosis.[9] There are also indications that premature infants have a limited dietary supply of the n-3 FAs required for normal composition of the brain and retinal lipids.[10,11]

Little is known about the effects of intravenously administered ω-3 FAs. A parenteral fish oil preparation had no apparent influence on growth and nitrogen metabolism in catabolic rats.[12] However, it resulted in a decrease of plasma free-FA concentration and liver triglyceride content, suggesting increased FA oxidation and reduced liver triglyceride synthesis. In rats, parenteral fish oil feeding induced a dose-dependent incorporation of ω-3 FAs into tissue total lipids and phospholipids at the expense of ω-6 FAs as early as 3 to 4 days after starting the infusion.[12]

According to recent studies, leukocytes might be a useful alternative as an easily accessible and (after isolation) viable homogeneous cell model enabling study of intracellular metabolism. In patients with active Crohn's disease, daily infusion of EPA (0.6 g) influenced the generation of LTs in polymorphonuclear leukocytes.[13] Accordingly, in the present study, we investigated the effect of parenteral ω-3 FAs on the plasma and membrane FA composition and LT-synthesizing capacity of peripheral leukocytes in patients during postoperative stress.

SUBJECTS AND METHODS

Patients and Nutrition

Twenty patients (10 men and 10 women aged 42 to 69 years) undergoing major abdominal surgery were investigated. Clinical data for all patients are summarized in Table 1. Patients with manifest metabolic disease (eg, diabetes mellitus or hyperthyroidism), chronic renal or liver disease, or contraindications against parenteral fat emulsions were excluded. Patients treated with nonsteroidal antiinflammatory drugs, steroids, or calcium antagonists within 2 weeks prior to the study were excluded. The study was approved by the Ethics Committee of the medical faculty of Ruhr-University of Bochum, and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1989. Voluntary informed consent of each patient was obtained before commencement of the investigation.

Patients were randomly assigned to two equal groups to receive isonitrogenous (0.24 g $N \cdot kg^{-1} \cdot d^{-1}$) and isoenergetic (92 kJ/22 kcal $\cdot kg^{-1} \cdot d^{-1}$) total parenteral nutrition (TPN) over 5 days. The regimen consisted of 1.5 g amino acids $\cdot kg^{-1} \cdot d^{-1}$, 3 g glucose $\cdot kg^{-1} \cdot d^{-1}$, and 1 g fat $\cdot kg^{-1} \cdot d^{-1}$. Lipid nutrition consisted of either the soybean oil emulsion ([SO] Lipovenös 20%; Fresenius AG, Bad Homburg, Germany) or a novel fish oil emulsion ([FO] Omegavenös 10%; Fresenius). In the FO diet, 0.15

From the Department of Anesthesiology and Intensive Care Medicine and the Department of Experimental Clinical Medicine, Ruhr-University of Bochum, Bochum; and the Institute of Biological Chemistry and Nutrition, University of Hohenheim, Stuttgart, Germany.

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Address reprint requests to Bart J. Morlion, MD, Department of Anesthesiology and Intensive Care Medicine, Marienhospital Herne, Ruhr-University of Bochum, Hoelkeskampring 40, 44625 Herne, Germany.

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Table 1. Clinical Data for Patients Admitted to the Study

Group	Age (yr)	Sex	Height (cm)	Weight (kg)	Condition
SO	51	M	176	80	Carcinoma of the rectum
	59	M	174	77	Duodenal ulcers
	46	F	163	56	Carcinoma of the sigmoid colon
	75	F	160	67	Carcinoma of the sigmoid colon
	52	F	159	47	Gastric ulcer
	52	F	172	48	Carcinoma of the sigmoid colon
	56	M	168	70	Carcinoma of the colon
	70	F	164	75	Non-Hodgkin's lymphoma (stomach)
	56	M	176	85	Carcinoma of the sigmoid colon
	61	F	163	70	Carcinoma of the sigmoid colon
Mean ± SEM	58 ± 2.8		168 ± 1.9	67.6 ± 4.1	
FO	53	F	165	72	Uterus myomatosis
	70	F	168	72	Carcinoma of the stomach
	64	M	168	83	Carcinoma of the sigmoid colon
	64	M	171	85	Carcinoma of the colon
	64	M	180	85	Carcinoma of the colon
	51	F	160	49	Gastric ulcer
	71	M	173	71	Carcinoma of the colon
	69	F	168	65	Carcinoma of the rectum
	35	M	176	87	Diverticulitis of the sigmoid colon
	41	M	180	63	Diverticulitis of the sigmoid colon
Mean ± SEM	58 ± 4.1		170 ± 1.9	73.1 ± 3.9	

g fish oil was substituted for soybean oil, with the composition otherwise being the same. The content of C20:5n-3 (EPA) and C22:6n-3 (DHA) in the FO emulsion was 2.3% and 3.9%, respectively, with trace amounts (0.18%) of C20:4n-6 (AA). The amount of C18:2n-6 (linoleic acid) was 46.3%, essentially the same as found in the SO emulsion (54%). Peripheral venous blood samples were obtained before surgery at 8 AM and on the first postoperative day before the start of TPN. Further blood samples were collected on the third day after surgery, on TPN, on the sixth day at completion of TPN, and on the eighth and 14th days postoperatively on enteral/oral nutrition.

Analytical Methods

Authentic LTC_4 used as a standard was a generous gift from Dr A.W. Ford Hutchinson of Merck Frosst Laboratories (Point Claire/Dorval, Canada). All other LT standards were purchased from Paesel & Lorei (Hamburg, Germany). Calcium ionophore A23187 was from Sigma (St Louis, MO). [14,15-^{3}H] LTC_4 was obtained from New England Nuclear (Dreieich, Germany). Sep-Pak C_{18} cartridges were obtained from Waters (Milford, CT). LiChrosphere 60-RP-select B C_{18} columns and acetylchloride were from Merck (Darmstadt, Germany), and Nucleosil C_{18} columns were from Macherey & Nagel (Düren, Germany). All solvents (high-performance liquid chromatography [HPLC] grade) were obtained from Baker (Deventer, The Netherlands).

Leukocytes. Ten milliliters of heparinized (20 U/mL) venous blood was sedimented through 6% dextran 500 at room temperature for 45 minutes. Leukocyte-rich plasma was centrifuged at 200 × *g* for 10 minutes at 4°C. Remaining erythrocytes were removed by hypotonic lysis followed by centrifugation.

LT formation. The cell pellet was suspended in phosphate-buffered saline (0.01 mol/L, pH 7.4) containing glucose (0.1%) and $CaCl_2$ (0.88 mmol/L), counted, and adjusted to 1×10^6 leukocytes/mL. Viability of the leukocyte preparation was greater than 96% as assessed by trypan blue dye exclusion. Aliquots (500 μL) were preincubated for 20 minutes at 37°C, and then ionophore A23187 was added at a final concentration of 5 μmol/L to stimulate LT generation. Three repetitive incubations were performed for each sample. Control incubations without addition of ionophore were included in each experiment. The incubations were stopped after 20 minutes by rapid cooling on ice. Cell-free supernatants were stored at −80°C until analysis.

Membranes. The cell pellet was suspended with Hanks balanced salt solution to 2.5 to 5×10^6 leukocytes/mL. Aliquots (500 μL) were stored under nitrogen at −80°C until analysis.

Plasma. EDTA blood (4 mL) was centrifuged (1,550 × *g* for 10 minutes at 4°C), and 500-μL aliquots of plasma were overlaid with nitrogen and stored at −80°C until analysis.

Analyses. LTs were analyzed using a combined reversed-phase HPLC radioimmunoassay method. Sulfidopeptide LTs were first separated by reversed-phase HPLC according to the method described by Simmet et al[14] and subsequently quantified by radioimmunoassay. Briefly, 2-mL aliquots of pooled incubations were extracted using Sep-Pak C_{18} cartridges conditioned with ethanol (20 mL) followed by distilled water (20 mL) and distilled water containing 0.1% EDTA (15 mL). After washing with hexane (5 mL), LTCs were eluted with 5 mL methanol. The solvents were evaporated under reduced pressure, and the residues were taken up in 0.1 mL methanol:water (30:70 vol/vol) and separated by HPLC (LiChrosphere 60-RP-select B C_{18} columns: particle size, 5 μm; solvent system, methanol:water:acetic acid 65:35:0.1 vol/vol, containing 1 mmol/L EDTA, pH 5.6, adjusted with NH_4OH; flow rate, 1 mL/min; wavelength, 280 nm). The eluates were collected in 1-minute fractions and evaporated under reduced pressure, and the residues were taken up in 0.5 mL Tris hydrochloride buffer containing 1 mg/mL gelatin. Following the HPLC separation, aliquots were analyzed for LTC_4 and LTC_5 content by radioimmunoassay using an antibody recognizing LTC_4 and LTC_5 to the same extent. Recovery rates were equal for LTC_4 and LTC_5 (65% to 75%). The sensitivity and specificity of the assay have been described previously.[15] Retention times of immunoreactive materials were compared with retention times of standard LTs.

LTB and ω-oxidated products. LTB and ω-oxidized products were analyzed by HPLC as described previously,[16] but two alternative solvents were used stepwise during the chromatography. Briefly, pooled supernatants of incubations (2 mL) were deprotein-

ized by addition of 3 mL methanol:acetonitrile (50:50 vol/vol), overlaid with nitrogen, and frozen at −20°C for 12 hours. After centrifugation (1,000 × *g* for 15 minutes), the supernatants were lyophilized, suspended in 600 μL methanol:water (30:70 vol/vol), overlaid with nitrogen, and stored at −20°C for 2 hours.

Thawed samples were centrifuged (9.7 × *g* for 2 minutes at room temperature), and 200 μL was then applied to the reversed-phase HPLC column (Nucleosil C_{18} column: particle size, 5 μm; flow rate, 1 mL/min). The solvent system consisted of buffer A (0 to 5 minutes, elution of 20-OH-LTB_5 and 20-COOH-LTB_5): phosphate buffer (13.8 mmol/L KH_2PO_4 containing 0.0235% EDTA): acetonitrile:methanol (60:24:16 vol/vol) and buffer B (6 to 40 minutes, elution of LTB_5, LTB_4, 20-OH-LTB_4, and 20-COOH-LTB_4):phosphate buffer (17.8 mmol/L KH_2PO_4 containing 0.03% EDTA):acetonitrile:methanol (50:30:20 vol/vol). pH was adjusted to 5.0 with phosphoric acid. Detection and identification of LTs was performed at 280 nm, and peak areas were calculated with a chromatography data system (Series 3000; Nelson Analytical, Mannheim, Germany).

Leukocyte membrane and plasma FA composition. Lipids were extracted with chloroform:methanol (1:1 vol/vol) containing 50 mg/L butylhydroxytoluol (BHT). Margaric acid 0.1 mg was added to the samples as an internal standard. The chloroform phase was dried under a nitrogen stream and resuspended in 2 mL methanol: hexane (4:1 vol/vol, containing 50 mg/L BHT). Acetylchloride (0.2 mL) was added to the samples drop by drop. After a 60-minute incubation in a shaking water bath at 100°C, samples were cooled and dissolved with 5 mL 6% K_2CO_3. After centrifugation (2,600 × *g* for 10 minutes at 4°C), the hexane-containing upper phase could be analyzed by gas chromatography. FAs were chromatographed as methyl esters on a 30-m fused silica column (biscyanopropylpolysiloxan). Analysis was performed on a Perkin-Elmer (Norwalk, CT) Sigma 2000 gas chromatograph with a flame ionization detector (250° to 270°C). Nitrogen was used as the carrier gas and helium (flow, 30 mL/min) and compressed air (flow, 150 mL/min) as the make-up gas. The injection port temperature was 200°C and detector temperature 250°C. The column temperature was held at 150°C for 8 minutes and in stepwise fashion reached a plateau of 220°C. Samples (1 μL) of the hexane phase were injected by autosampler or manually. Peaks were identified by comparison of retention times of a chromatographed mixture of standard FAs.

Statistical Analysis

Values are presented as the mean ± SEM. Statistical analysis was performed by multivariate ANOVA and Wilcoxon matched-pairs signed-rank test. Significance level was *P* less than .05.

RESULTS

All 20 patients included in the study completed the trial. Laboratory tests were normal, and no side effects or complaints were noted. None of the patients showed a bleeding tendency. The FA composition of leukocyte membrane phospholipids is shown in Table 2. EPA and DHA were increased on day 6 in the FO group, and normalized to the preoperative level after discontinuation of FO supplementation (day 8). Following surgical trauma, the concentration of AA increased in both treatment groups. On day 6, the concentrations of EPA and DHA were different from those seen in the SO group.

The FA composition of plasma phospholipids is shown in Table 3. An elevation of plasma phospholipid EPA, DHA, and α-linolenic acid (α-LA) was observed on days 3 and 6 (EPA and DHA also on day 8) with FO treatment, yet both ω-3 FAs decreased after completion of the supplemented FO on day 8 compared with day 6. Leukocytes incubated in the absence of ionophore A23187 do not release measurable amounts of LTC_4 and LTC_5. γ-LA increased on days 3 and 6 and AA decreased on days 6 and 8 in response to FO infusion. EPA and DHA were higher in the FO group on days 6 and 8 (EPA also on day 3) than in the SO group. In the latter group, only α-LA increased due to infusion of this FA with the emulsion. Similar to the FO group, AA decreased with SO treatment on days 3 and 6.

The LT-synthesizing capacity of activated leukocytes is shown in Fig 1. There were no differences in the amount of LTB_4, LTB_5 and LTC_4, LTC_5, respectively, generated by activated leukocytes prior to nutrition. In patients treated with the SO emulsion, no differences in leukocyte generation of LTB_4, LTB_5, LTC_4, and LTC_5 were observed. Leukocytes from patients treated with FO synthesized enhanced amounts of LTC_5 and LTB_5, showing an obvious increasing trend (nonsignificant) during the treatment period. However, there was no difference with FO in the amount of LTB_4 and LTC_4 generated on days 0, 3, 6, 8, and 14 (data in Fig 1 are for days 0, 6, and 14 only).

DISCUSSION

The modulation of eicosanoid and cytokine biology by nutrients provides, in theory, an intervention strategy for

Table 2. FA Composition of Leukocyte Membrane Phospholipids Before and During TPN With SO or FO

TPN	Day 0	Day 1	Day 3	Day 6	Day 8	Day 14
SO						
C18:2n-6	3.38 ± 0.63	4.04 ± 0.69	3.86 ± 0.59	4.03 ± 0.48	4.48 ± 0.56	4.30 ± 0.55
C20:4n-6	2.05 ± 0.52	3.52 ± 0.79*	2.31 ± 0.39‡	2.26 ± 0.41‡	2.29 ± 0.35‡	2.47 ± 0.45‡
C20:5n-3	0.90 ± 0.22	1.14 ± 0.36	0.95 ± 0.21	0.92 ± 0.24	0.84 ± 0.18	0.95 ± 0.29
C22:6n-3	0.73 ± 0.25	2.05 ± 0.50†	1.42 ± 0.24*	1.09 ± 0.19	1.51 ± 0.44	1.39 ± 0.22
FO						
C18:2n-6	2.10 ± 0.37	3.18 ± 0.48	3.50 ± 0.50	3.93 ± 1.02	3.54 ± 0.77	2.98 ± 0.42
C20:4n-6	2.11 ± 0.27	2.70 ± 0.35	2.10 ± 0.35	2.66 ± 0.40	2.03 ± 0.40‡	2.10 ± 0.34‡
C20:5n-3	0.65 ± 0.14	0.87 ± 0.21	1.06 ± 0.20	1.65 ± 0.56*	0.61 ± 0.09	0.77 ± 0.17
C22:6n-3	1.51 ± 0.40	1.96 ± 0.43	1.66 ± 0.30	2.41 ± 0.81	1.55 ± 0.41	1.39 ± 0.25

NOTE. Phospholipids are shown as percent of total FAS.

*$P < .05$, †$P < .01$: *v* day 0.

‡$P < .05$ *v* day 1.

Table 3. FA Composition of Plasma Phospholipids Before and During TPN With SO or FO

TPN	Day 0	Day 1	Day 3	Day 6	Day 8	Day 14
SO						
C18:2n-6	27.95 ± 1.15	25.53 ± 1.31	28.77 ± 0.98	29.26 ± 1.24	27.32 ± 1.34	27.12 ± 0.92
C18:3n-6	0.25 ± 0.03	0.33 ± 0.15	0.50 ± 0.11	0.55 ± 0.11	0.57 ± 0.09	0.40 ± 0.06
C18:3n-3	0.40 ± 0.05	0.39 ± 0.07	0.76 ± 0.15	0.92 ± 0.18*	0.57 ± 0.09	0.45 ± 0.06
C20:4n-6	4.64 ± 0.68	4.65 ± 0.60	3.84 ± 0.54‡	3.41 ± 0.51‡	3.51 ± 0.49‡	3.90 ± 0.50†
C20:5n-3	0.52 ± 0.06	0.53 ± 0.06	0.42 ± 0.05**	0.46 ± 0.09***	0.40 ± 0.03***	0.54 ± 0.06#
C22:6n-3	2.08 ± 0.20	2.11 ± 0.19	2.18 ± 0.24¶	2.09 ± 0.19**	1.84 ± 0.14**	1.88 ± 0.19
FO						
C18:2n-6	23.74 ± 0.79	23.27 ± 0.84	24.15 ± 0.81	24.74 ± 0.85	22.24 ± 1.17	25.54 ± 1.35
C18:3n-6	0.24 ± 0.04	0.19 ± 0.03	0.53 ± 0.12†	0.50 ± 0.05†	0.43 ± 0.05	0.49 ± 0.07
C18:3n-3	0.34 ± 0.04	0.30 ± 0.05	0.64 ± 0.07‡	0.59 ± 0.06‡	0.46 ± 0.03	0.37 ± 0.04
C20:4n-6	4.70 ± 0.60	5.06 ± 0.63	4.25 ± 0.54	3.70 ± 0.36‡	3.38 ± 0.37‡	3.99 ± 0.41†
C20:5n-3	0.74 ± 0.14	0.65 ± 0.10	1.22 ± 0.11*	1.89 ± 0.14†	1.21 ± 0.1*§	0.80 ± 0.06
C22:6n-3	2.19 ± 0.20	2.13 ± 0.18	2.90 ± 0.15‡	3.30 ± 0.11‡	2.53 ± 0.14‖	2.21 ± 0.11

NOTE. Phospholipids are shown as percent of total FAs.
*$P < .05$, †$P < .01$, ‡$P < .001$: *v* day 0.
§$P < .01$, ‖$P < .001$: *v* day 6.
¶$P < .05$, #$P < .01$, **$P < .001$: SO *v* FO.

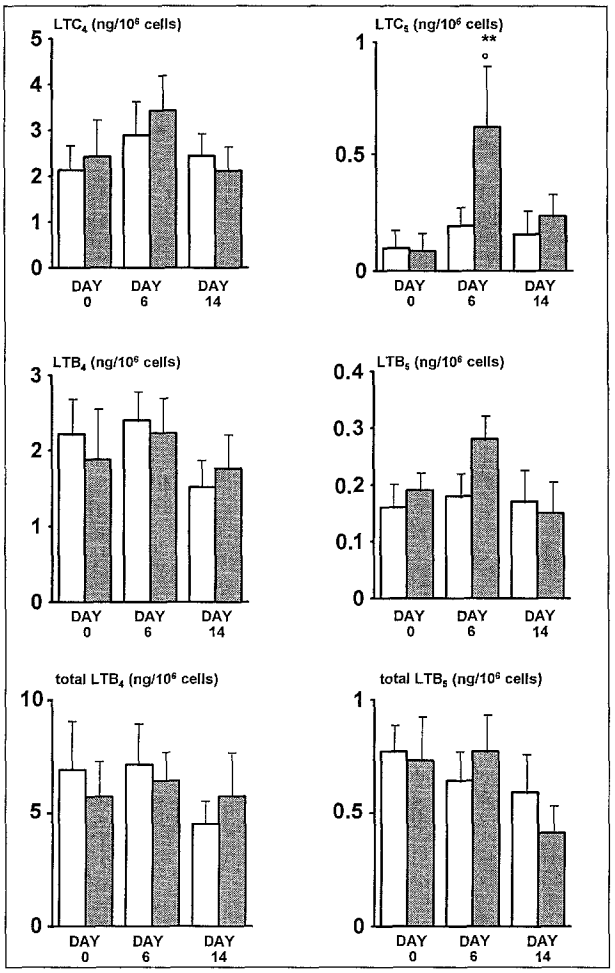

Fig 1. In vitro LT-synthesizing capacity of human peripheral blood leukocytes after stimulation with A23187 (5 μmol/L). Patients received TPN without fish oil (□, n = 10 [SO]) or with fish oil (▨, n = 10 [FO]). Results are the mean ± SEM. °$P < .05$, FO *v* SO; **$P < .01$, day 6 *v* day 0.

manipulating events so that cytokines and eicosanoids can express their beneficial effects rather than their potentially damaging properties in patients.[2,17] To evaluate the possible immunomodulatory effects of fish oil in parenteral nutrition, we investigated the effect of FO supplementation on plasma and peripheral leukocyte membrane FA composition and LT-synthesizing capacity of leukocytes in patients with postoperative trauma. Patients undergoing major uncomplicated abdominal surgery were recruited for this study to establish a group of patients comparable with respect to postoperative stress metabolism, catabolism, and the need for TPN (Table 1). Infusion of the FO lipid emulsion was without side effects, and no complaints were noted.

Simultaneously with the observed incorporation of ω-3 FAs in phospholipids, the synthesizing capacity of LTC_5 and presumably also LTB_5 increased with FO infusion. This, together with the increased EPA and DHA concentrations in the presence of reduced AA content, indicates a high activity of the 5-lipoxygenase pathway. However, no decrease was found in the generation of LTB_4 and LTC_4, which might be expected, considering the competition between the substrates of 5-lipoxygenase and AA. As previously reported, AA is sensitive to catabolic stress.[18] In accordance with this observation, increased AA concentrations were found in the present study following surgery. The response to the two lipid nutritional regimens was well reflected in the recovered FA contents of plasma phospholipids and leukocyte membrane phospholipids. Following FO infusion, augmented EPA and DHA contents were observed in the membrane phospholipids, and as a consequence, AA concentrations declined and remained low as long as the higher ω-3 FA content persisted (Tables 2 and 3).

Nevertheless, our results are in accordance with the results reported by Ikehata et al,[13] who showed a 1.8-fold increase of LTB_5 without a decrease of LTB_4 after daily infusion of approximately 10 $mg \cdot kg^{-1} \cdot d^{-1}$ EPA in pa-

tients with active Crohn's disease.[13] The considerable elevation (sevenfold) in LTC_5 production in the face of the modest increase in LTB_5 formation (Fig 1) might be attributable to a difference in the affinity of the LT-forming enzymes (LTB_5-hydrolase and LTC_5-synthase) for the substrate (LTA_5). It has been reported that the LTC series is chiefly synthesized by the eosinophil,[19] and differences in the counts of these cells may thus severely influence the results obtained. However, in the present study, eosinophil counts were carefully controlled—there was virtually no variation in the number of these cells.

It has been demonstrated that enteral provision of LA reduces the incorporation of dietary EPA into rat and human neutrophil membranes[20,21]; simultaneously, production of LTB_4 is diminished.[21] One could speculate as to whether higher membrane EPA concentrations may be reached without coadministration of LA and whether this would possibly increase the formation of LTB_5 and LTC_5 and decrease the formation of LTB_4 and LTC_4. In our study, both groups of patients received a substantial amount of LA as part of the lipid emulsions, which may have limited the incorporation of EPA in leukocyte membranes. This high background of ω-6 FAs might explain why we could not confirm herein the triglyceride-lowering effect of fish oil, as observed in the rat. Although the 8% α-LA administered cannot be desaturated and elongated to EPA in leukocytes,[22] it can be metabolized to EPA in hepatic tissue. This might serve as an explanation for the unexpected tendency of increased LTB_5 and LTC_5 production in the patients not treated with FO.

We conclude that a 5-day parenteral FO supplementation is accompanied by an immunomodulatory effect on lipid-mediator generation in peripheral leukocytes during postoperative trauma. The question might be raised as to how this treatment provides beneficial outcomes. According to current opinion, it is not the absolute concentration but rather the ratios of LTs, particularly LTB_4/LTB_5 and LTC_4/LTC_5, that are of major concern. It is currently claimed that modulation of the LTB_4/LTB_5 ratio may influence several biosynthetic processes at the cellular level.[23] Thus, tumor necrosis factor mRNA expression is increased and interleukin-2 and interleukin-6 mRNA expression is suppressed with high and low ratios of four series of LTs, respectively.[24-27] This implies that a low ratio, as found in the present study, may be associated with attenuation of a possible inflammatory reaction. This, of course, might be considered beneficial. The therapeutic benefit and clinical outcome, optimum amount of ω-3 FAs, and ideal ratio of ω-3 to ω-6 FAs remain to be determined in further investigations.

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