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ORIGINAL ARTICLE

Olive oil is more potent than fish oil to reduce septic pulmonary dysfunctions in rats

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Abstract
Background Abdominal sepsis is frequently the cause of severe pulmonary dysfunction. Via the thoracic duct, the lung is the first organ exposed to gut-derived mediators released into the mesenteric lymph.
Aim The aim of this study is to investigate whether an enteral immunonutrition with long chain triglycerides prevents septic pulmonary dysfunctions.
Materials and methods Mesenteric lymph was obtained from lymph fistula *donor rats* during sepsis (lipopolysaccharides [LPS], 5 mg/kg i.p.) with or without enteral immunonutrition (1% of olive oil or 1% of fish oil). Sepsis lymph was then reinfused into the jugular vein of *separate recipient* rats. Thereafter, the lung tissue was analyzed for the distance of oxygen diffusion, inflammatory response, and cell apoptosis.
Results Sepsis significantly increased TNFα release into the mesenteric lymph, whereas an enteral immunonutrition with olive oil significantly reduced the TNFα release into the mesenteric lymph by more than five-fold. Sepsis lymph induced a significant increase in alveolar wall thickness, inflammatory reaction, and apoptosis; whereas sepsis lymph collected during olive oil resorption prevented the thickening of the alveolar walls and induced only a mild inflammation, being more potent than fish oil to reduce septic pulmonary dysfunction.
Conclusions Mediators in the sepsis lymph induce pulmonary dysfunction. The lung may be protected by an enteral immunonutrition containing long chain triglycerides such as olive oil.

Keywords Mesenteric lymph · Lung · Sepsis · Olive oil

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Introduction

Recent studies investigating the role of the gut in multiple organ dysfunction syndrome (MODS) during an acute insult to the gastrointestinal tract, such as trauma–hemorrhagic shock or sepsis, indicated its significance in producing inflammatory mediators that are drained into the systemic circulation causing systemic inflammatory responses and acute lung injury [1, 2]. The hypothesis of MODS because of bacterial translocation has been expanded. Many studies have demonstrated that gut-derived nonbacterial inflammatory agents are responsible for acute lung injury during an acute insult to the gastrointestinal tract [3, 4].

The gastrointestinal tract contains the largest lymphatic system of the body [5]. Mediators released from inflammatory cells activated during an acute insult are released into the interstitium, which is predominantly drained by lymphatics [5]. It has been demonstrated that the lymphatics of the gut play an important role in mediating distant organ injury during trauma–hemorrhagic shock. Diversion of these gut-derived factors by the interruption of the mesenteric lymphatics prevented acute lung injury, neutro-

phil activation, endothelial cell apoptosis as well as red blood cell dysfunction [6–8].

Leite et al. [9] has recently demonstrated that an enteral nutrition containing olive oil is beneficial regarding the survival during sepsis in mice, and there are preliminary data that an enteral immunonutrition with a lipid formula enriched with fish oil can ameliorate septic pulmonary dysfunction in a rat model (unpublished data).

Recently, we developed a new animal model to investigate the release of mediators into the mesenteric lymph during sepsis. We have shown that during abdominal sepsis, inflammatory mediators like tumor necrosis factor-α (TNFα) are released in high concentrations into the mesenteric lymph—an indication that TNFα is a good parameter to monitor the release of inflammatory mediators from the gut into mesenteric lymph during sepsis [1]. Reinfusion of the sepsis lymph (SL) into separate recipient rats induced a significant thickening of the alveolar walls, serving as a parameter for increased oxygen transport as well as a significant invasion of inflammatory cells serving as parameters of the inflammatory response (unpublished data).

The aim of the present study was to distinguish which enteral immune-modulating nutrition containing long chain triglycerides, either a source of olive oil or a mixture of soybean/fish oil, is able to reduce septic pulmonary dysfunctions more sufficiently in a rat model.

Materials and methods

Animals

Male Sprague–Dawley rats (Charles River, Kieslegg, Germany), maintained on regular laboratory chow, were housed under controlled conditions of illumination (12:12-h light/dark cycle starting at 07:00 P.M.), humidity, and temperature (21°C). Rats were fasted overnight but allowed water ad libitum before all surgical and experimental procedures. The institutional guidelines for the care and use of laboratory animals were followed throughout the study.

Mesenteric lymph collection

The method of mesenteric lymph duct cannulation has been previously published by the authors [1, 10]. In brief, rats (260–300 g) were anesthetized with methohexital sodium (60 mg/kg i.p.; Brevital, Jones Pharma, St. Louis, MO), and the superior mesenteric lymph duct was cannulated with a polyvinyl tube (Medical grade, 0.50 mm ID, 0.80 mm OD, Dural Plastics, Australia) fixed in place with a drop of cyanoacrylate glue (Krazy Glue, Elmers Products, Columbus, OH) and externalized through the right flank. A second tube (Silastic 1 mm ID, 2.15 mm OD) was passed through the fundus of the stomach, extended 3 cm into the duodenum, secured in place with a silk suture, and externalized through the left flank. After surgery, rats were placed in restrain cages, and a glucose–saline solution (glucose 0.2 mol/l, NaCl 145 mmol/l, and KCL 4 mmol/l with or without lipid [1% ClinOleic {CLINO}, Baxter, Munich, Germany or 1% SMOF lipid, Fresenius Kabi, Bad Homburg, Germany]) was infused continuously through the duodenal cannula at a rate of 3 ml/h to equalize volume and energy losses via the lymph. A steady lymph flow of 2.5±0.5 ml/h confirmed a nonobstructive lymph flow, and that the cannula was appropriately positioned. CLINO lipid contains mainly ω-9 fatty acids in the form of olive oil (80%) and ω-6 fatty acids in the form of soy oil (20%); whereas SMOF lipid is enriched in ω-3 fatty acids in the form of fish oil (15%) and additionally contains medium chain triglycerides (30%), ω-6 fatty acids in the form of soy oil (30%), and ω-9 fatty acids in the form of olive oil (25%).

Mesenteric lymph was collected from three different experimental groups as follows:

1. SL: rats were intestinally infused with a glucose–saline solution and LPS (*Escherichia coli* serotype 0111:B1, Sigma, 5 mg/kg in 1 ml) and was injected i.p. after the recovery period (n=6).
2. SL–CLINO lymph: rats were intestinally infused with 1% of CLINO lipid, and LPS was injected i.p. after the recovery period (n=6).
3. SL–SMOF lymph: rats were intestinally infused with 1% of SMOF lipid, and LPS was injected i.p. after the recovery period (n=6).

Mesenteric lymph was continuously collected after a steady lymph flow of 2.5 ml occurred for a 12-h collection period in 2-h time intervals in all above-mentioned groups. Lymph was collected in ice-chilled tubes, centrifuged, frozen, and stored at −80°C for further experiments.

Detection of mediators in mesenteric lymph

SL, SL–CLINO, and SL–SMOF lymph were taken in 2-h time intervals for the detection of the proinflammatory cytokine TNFα (ELISA kit, no. KRC 3012, Biosource, CA) to monitor adequate septic responses after i.p. LPS injections.

Mesenteric lymph infusion

The lymph samples of all six donor rats of each group were pooled for the collection period of 1–12 h. The mesenteric lymph was then reinfused into separate groups of healthy recipient rats through a catheter in the jugular vein (PE10, SIMS Portex, UK). Either NaCl, SL, SL–CLINO or SL–SMOF lymph was infused for 90 min in fasted recipient

rats at an infusion rate of 2.0 ml/h (n=6/group). The lung was harvested immediately after the termination of lymph infusion and fixed in paraformaldehyde (4%, Sigma, Steinheim, Germany) for histological staining.

Histological analysis of lung tissue

Lung tissue was embedded in paraffin and cut in 1-μm sections. It was stained for either hematoxylin eosin (H&E) or H&E in combination with myeloperoxidase (MPO) or TUNEL. For each animal, 30 optical sections (24,300 μm^2) were analyzed with the Quantimet System (Leica, magnification 40×) for the thickness of the alveolar walls (parameter of oxygen diffusion), the MPO positive cells (parameter of inflammation), and the TUNEL positive cells (parameter for permanent damage).

The MPO immunohistochemistry was performed in paraffin-embedded lung tissue, which was washed consecutively in xylol and ethanol. The endogenous peroxidase was blocked by preincubation with hydrogen peroxide, and nonspecific background staining was blocked by incubation with 20% swine serum. Thereafter, the tissue was incubated overnight with a rabbit anti-MPO antibody (1:50, Dianova, Germany) at room temperature. The tissue was then washed in phosphate-buffered saline and incubated with a biotinylated swine anti-rabbit antibody (1.600, Dako, Germany) for 60 min at room temperature. MPO immunoreactivity was demonstrated by the avidin-biotin-complex method with 3.3′diaminobenzidine serving as chromagen.

TUNEL-positive cells were detected using the *In situ cell death detection kit* (POD, Roche, Penzberg, Germany).

Statistical analysis

Data are presented as mean±standard error of the mean. Differences between independent groups were determined by a two-tailed unpaired Student's t test, and differences within a group were determined by a two-tailed paired Student's t test using the software package of GraphPad Prism 3.02 (San Diego, CA). For multiple comparisons, values were adjusted according to Bonferroni. A probability of $p<0.05$ was taken as significant.

Results

Effects of an enteral immunonutrition with long chain triglycerides on TNFα release into mesenteric lymph during sepsis

Sepsis significantly increased the inflammatory mediator release like TNFα into the mesenteric lymph compared to baseline levels by more than 200-fold within the first 2 h (TNFα pg/ml; baseline, 44±12; SL 1±2 h, 10,683±1,402*; 3+4 h, 4,784±2,145*; 5+6 h, 105±27; *$p<0.05$ vs baseline). An enteral immune-modulating diet containing 1% of CLINO significantly reduced the TNFα release into the mesenteric lymph during sepsis by more than fivefold compared to the SL within the first 2 h after sepsis was induced (TNFα pg/ml; baseline, 33±15; SL–CLINO 1+2 h, 2,330±1,279*; 3+4 h, 897±662; 5+6 h, 75±26; *$p<0.005$ vs SL at corresponding time intervals). One percent of SMOF, however, failed to reduce the TNFα release into the mesenteric lymph during sepsis (TNFα pg/ml; baseline, 39±25; SL–SMOF 1+2 h, 12,133±5,287; 3+4 h, 2,426±1,739; 5+6 h, 236±113).

Anatomical changes in the lung parenchyma of recipient rats after infusion of SL from lymph fistula donor rats

The thickness of the alveolar walls significantly increased by approximately threefold in recipient rats after the infusion of SL compared to the infusion of physiological saline (thickness of alveolar walls [μm]: NaCl, 4.9±0.16; SL, 15.1±0.44*; *$p<0.001$ vs NaCl). Infusion of the SL obtained during enteral immunonutrition with either CLINO or SMOF lipid, significantly reduced the thickness of the alveolar walls in the lungs of the recipient rats compared to the SL collected with no immunonutrition (thickness of alveolar walls [μm]: SL, 15.1±0.44; SL–CLINO, 5.1±0.16*$^{\#}$; SL–SMOF, 7.6±0.27*; *$p<0.001$ vs SL; $^{\#}p<0.001$ vs SL–SMOF). However, the SL collected during CLINO resorption was more potent to inhibit the thickening of the alveolar walls compared to the SL obtained during SMOF-lipid resorption (Figs. 1 and 2).

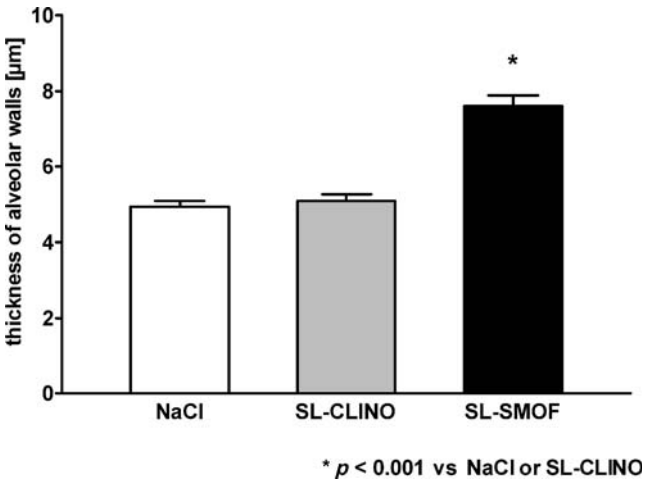

Fig. 1 SL collected during CLINO resorption (SL–CLINO, *gray bar*) was significantly more potent to reduce the thickening of the alveolar walls compared to the SL collected during SMOF-lipid resorption (SL–SMOF, *black bar*) and compared to the control group infused with physiological saline (NaCl, *white bar*)

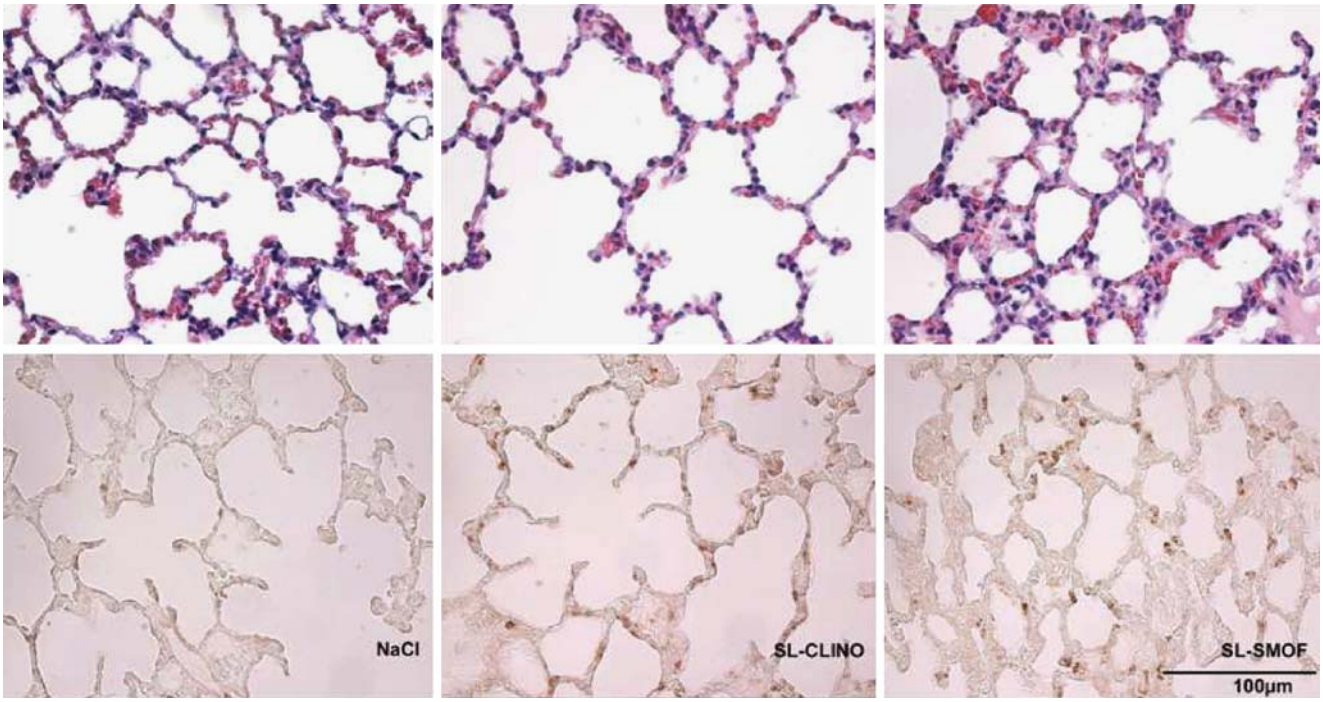

Fig. 2 Lung parenchyma of the control rats infused with NaCl is shown in the *left column*, lung parenchyma of the recipient rats infused with SL collected during an enteral immunonutrition with CLINO (SL–CLINO) is shown in the *middle column*, and lung parenchyma of the recipient rats infused with SL collected during SMOF-lipid (SL–SMOF) resorption is shown in the *right column*. The *upper row* shows lung parenchyma stained with H&E; the *lower row* shows lung parenchyma stained with MPO immunoreactivity. Infusion of SL–SMOF induced a markedly increased distance for oxygen diffusion, indicated by thickness of the alveolar walls, compared to SL–CLINO. Additionally, an increased inflammatory reaction, indicated by increased numbers of MPO positive cells, could be observed when SL–SMOF is infused compared to SL–CLINO. The *area of lung parenchyma* shown in this figure is approximately 2.5-fold larger than the optical sections used for the analysis in the present study. Images were taken at a magnification of 40×

Effects of an enteral immunonutrition on the invasion of immune cells into the lung parenchyma during sepsis

Infusion of the SL increased the number of MPO positive cells in the lungs of healthy recipient rats compared to the control group infused with physiological saline; in contrast, infusion of the SL obtained during enteral immunonutrition with either CLINO or SMOF lipid significantly reduced the inflammatory reaction in the lungs of recipient rats compared to the SL collected with no immunonutrition (number of MPO positive cells: SL, 53±1.4; SL–CLINO, 13±0.7*$^{\#}$; SL–SMOF, 25±0.8*; *p<0.001 vs SL; $^{\#}p$<0.001 vs SL–SMOF). Interestingly, the SL collected during CLINO resorption was more potent to inhibit the inflammatory response in the lungs of the recipient rats compared to the SL obtained during SMOF-lipid resorption (Figs. 2 and 3).

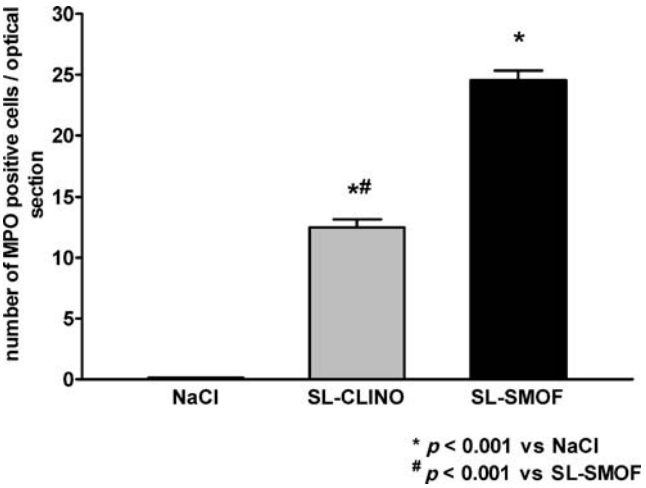

Fig. 3 The number of MPO positive cells in the lungs of the recipient rats was significantly increased after the infusion of the SL obtained during an enteral immunonutrition with either CLINO (SL–CLINO, *gray bar*) or SMOF lipid (SL–SMOF, *black bar*) compared to the control group infused with physiological saline (NaCl, *white bar*). However, SL collected during an enteral immunonutrition with CLINO was significantly more potent to reduce inflammation in the lungs of the recipient rats compared to SL collected during SMOF-lipid administration

Effects of an enteral immunonutrition on permanent lung injury during sepsis

The TUNEL positive cells in the lungs of healthy recipient rats were significantly increased after SL infusion compared to the control group infused with physiological saline. The SL obtained during enteral immunonutrition with either CLINO or SMOF lipid significantly reduced the cell

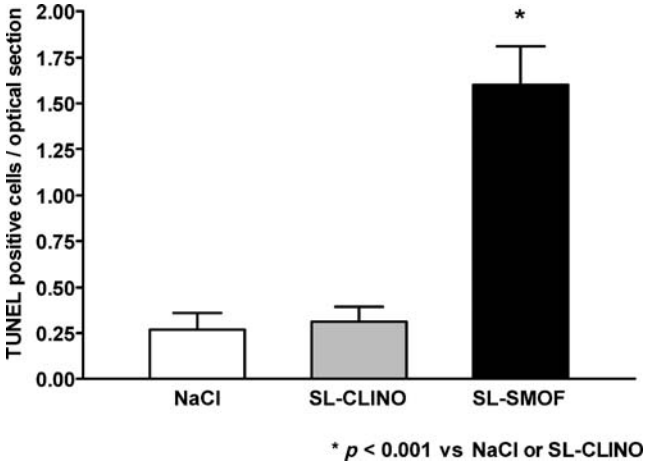

Fig. 4 The number of TUNEL positive cells in the lungs of the recipient rats was significantly increased after infusion of the SL obtained during an enteral immunonutrition SMOF lipid (SL–SMOF, *black bar*) compared to the control group infused with physiological saline (NaCl, *white bar*); whereas the SL collected during an enteral immunonutrition with CLINO (SL–CLINO) did not increase apoptosis in the lungs of the recipient rats

apoptosis in the lungs of recipient rats compared to the SL collected with no immunonutrition; however, the SL collected during CLINO resorption was more potent to inhibit cell apoptosis in the lungs of the recipient rats compared to the SL obtained during SMOF-lipid resorption (Fig. 4; number of TUNEL positive cells: NaCl, 0.27±0.09; SL, 12.48±2.3; SL–CLINO, 0.31±0.03*$^{\#}$; SL–SMOF, 1.6±0.21; *p<0.001 vs SL; $^{\#}p$<0.001 vs SL–SMOF).

Discussion

The present study demonstrates that inflammatory mediators are released from the gastrointestinal tract into the mesenteric lymph during sepsis, and that these inflammatory mediators are associated with septic pulmonary dysfunctions. An enteral immunonutrition containing mainly olive oil was able to reduce the inflammatory mediator release into the mesenteric lymph during sepsis. However, SMOF lipid, a fish oil-enriched lipid formula, failed to reduce inflammatory mediator release into the SL. We have demonstrated that the SL causes pulmonary dysfunction such as an increased distance for oxygen transport, inflammation, and cell apoptosis. The SL collected during an enteral immunonutrition with either an olive oil formula or a fish oil-enriched lipid formula significantly reduced the pulmonary dysfunction during sepsis. However, an enteral immunonutrition with olive oil more effectively reduced septic pulmonary dysfunction than with a fish oil-enriched lipid formula at the same concentration.

Sepsis is a common and severe disease in critically ill patients. In Germany, sepsis is the third most frequent cause of death after acute myocardial infarction [11]. MODS, including respiratory failure, is a typical consequence of severe sepsis. However, the pathophysiological mechanism of septic pulmonary dysfunction and the role of the gastrointestinal tract are not completely understood yet.

There is strong evidence that inflammatory mediators are released from the gastrointestinal tract during sepsis, and that these gut-derived mediators drained via the lymphatics into the systemic circulation are involved in mediating septic pulmonary dysfunction. It has recently been shown that the diversion of mesenteric lymph significantly increased pulmonary function and survival during sepsis or hemorrhagic shock [12]. The aim of the present study was to treat the gut with an immune-modulating diet during sepsis to decrease the inflammatory mediator release into the mesenteric lymph to improve pulmonary dysfunction during sepsis.

It has been shown in several clinical studies and different animal models that an immune-modulating diet containing long chain fatty acids was capable of improving survival and clinical outcome of critically ill patients [13]. The pathway by which an enteral immune-modulating diet with long chain fatty acids is mediating its anti-inflammatory effect remains uncertain. In the present study, we investigated the effect of CLINO and SMOF lipid on the inflammatory mediator release from the gastrointestinal tract during sepsis. CLINO contains 80% olive oil (ω-9 fatty acids) and 20% soybean oil (ω-6 fatty acids); whereas SMOF lipid is a fish oil-enriched lipid formula containing 15% fish oil (ω-3 fatty acids), 30% soybean oil (ω-6 fatty acids), 25% olive oil (ω-9 fatty acids), and 30% medium chain triglycerides.

ω-6 Fatty acids have been demonstrated to be metabolized by the elongation and desaturation into arachidonic acid, which serves as a precursor for more inflammatory four-series leucotriens and two-series prostaglandins like thomboxan A2 and prostaglandin I2, mediating vasoconstriction, bronchoconstriction, and increased blood clotting [14]. Similarly, ω-3 fatty acids are metabolized by the elongation and desaturation into eicosapentaenoic acid that serves as a precursor for both cyclooxygenase and lipoxygenase to synthesize the five-series leucotriens and the three-series prostaglandins such as prostaglandin I3 and thromboxan A3, which mediate vasodilatation, bronchodilatiation, and inhibition of the inflammatory cascade. Furthermore, ω-3 fatty acids reduce the proinflammatory effect of ω-6 fatty acids by inhibiting the enzyme desaturase, limiting the conversion of ω-6 fatty acids to arachidonic acid [15]. For the ω-9 fatty acids, it has been shown that they are able to reduce the synthesis of proinflammatory mediators like TNFα and therefore increase survival during endotoxic shock [9]. Furthermore, in colitis rats, it has been shown that feeding with ω-9 fatty acids in the form of olive oil reduced the inflammatory response in the colon [16].

It also possible that the lipid absorption and the chylomicron formation per se is involved in the immune-modulating effect of long chain triglycerides regardless of the structure of the fatty acid. Long chain triglycerides are absorbed by enterocytes, transformed into chylomicrons, released into the mesenteric lymph, and transported via the thoracic duct into the systemic circulation. Apolipoprotein A–IV (apo A–IV) is synthesized in the enterocytes during absorption of long chain fatty acids and packed into chylomicrons to reach water solubility. Apo A–IV has a distinct anti-inflammatory potency, as experimental colitis could be successfully treated by exogenous apo A–IV administration in mice [17].

A direct comparison of the two lipid formulas used in the present study is difficult, as the proportion of the lipid sources differs considerably as mentioned above. However, only CLINO (1%), containing 80% olive oil, was able to reduce the TNFα release into the mesenteric lymph during sepsis; whereas SMOF lipid (1%) enriched with fish oil failed to reduce TNFα in the SL. However, we have shown previously that SMOF at a higher dose (4%) is also able to reduce the TNFα release into the mesenteric lymph by about 4.5-fold similar to 1% of CLINO. The SL is likely a "cocktail" of gastrointestinal inflammatory and anti-inflammatory mediators released from the gut during sepsis, and therefore, TNFα is only one inflammatory cytokine among others increased in the SL. In the present study, we mainly measured TNFα in the SL to ensure the integrity of the sepsis model. Broad conclusions about the mediator release of the gut during sepsis therefore cannot be drawn, and the release of other inflammatory mediators remains speculative.

The main achievement of the present study was to demonstrate that an immune-modulating diet containing long chain triglycerides at a very low dose comparable to skim milk was able to reduce septic pulmonary dysfunctions. Interestingly, CLINO was also more sufficient to inhibit septic pulmonary dysfunction than SMOF lipid at the same dose. However, SMOF lipid at the dose of 4% was able to prevent septic pulmonary dysfunction similarly to 1% of CLINO (unpublished data). It remains to be determined which lipid source and which lipid structure is the most sufficient to inhibit septic pulmonary dysfunction being under investigation.

Conclusion

It has been demonstrated that the SL causes pulmonary dysfunction, such as increased distance of oxygen diffusion, inflammation, and permanent lung injury. An enteral immune-modulating diet containing olive oil was able to reduce the release of gut-derived mediators during sepsis. Furthermore, it could be demonstrated that the SL collected during an enteral immunonutrition containing an olive oil-enriched lipid formula was more potent than a fish oil-enriched lipid formula to reduce septic pulmonary dysfunction. An enteral immunonutrition containing olive oil might be a good supportive treatment in patients with abdominal sepsis to prevent pulmonary dysfunction.

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