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Parenteral Nutrition Facilitates Activation of Coagulation but Not of Fibrinolysis during Human Endotoxemia

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Venous thrombosis and bacterial infections are common complications of parenteral nutrition. To test the hypothesis that infection facilitates activation of coagulation during parenteral nutrition, healthy subjects were intravenously injected with endotoxin (2 ng/kg) after they had received either 1 week of standard parenteral nutrition (n = 7) or normal enteral feeding (n = 8). Compared with enteral feeding, parenteral nutrition was associated with a selectively enhanced activation of the coagulation system (plasma levels of thrombin-antithrombin III complexes) during endotoxemia. Activation of the fibrinolytic system (plasminogen activator activity, tissue-type plasminogen activator, plasminogen activator inhibitor type 1) proceeded similarly in both study groups. In patients receiving parenteral nutrition, one common complication (bacterial infection) may facilitate the occurrence of another common complication (venous thrombosis) by synergistic stimulation of the coagulation system.
or local irri a ion a he ca he er si e. Blood was ob ained before and 1, 1.5, 2, 3, 4, 5, 6, and 24 h af er adminis ra ion of endo oxin. Blood was also ob ained from paren erally fed volun eers before he ini ia ion of paren eral nu ri ion and 3 days hereaf er. All blood samples were cen rifuged a 4°C for 20 min a 1600 g and s ored a ~70°C un il assayed.

Assays. All assays were done in ci ra ed plasma samples. Co-agula ion ac iva ion was de ermined by measuring hrombin-an i-hrombin III (TAT) complexes (ELISA; Behringwerke, Marburg, Germany). Fibrinoly ic ac iva ion was moni ored by measuremen s of issue ype plasminogen ac iva or ( PA) by use of an ELISA, of plasminogen ac iva or inhibi or ype 1 (PAI-1) by use of an ELISA modified from an RIA, and of plasminogen ac iva or ac ivi y by use of an amidoli ic ay ass. All assays have been described in de ail previously [10, 11].

Statistical analysis. All values are given as means ± SE. Com- parisons wi hin and be ween groups were done by analysis of variance followed by Newman-Keuls es for mul iple comparison where appropria e. P < .05 was considered a s a isally signifi- can difference.

Results

Adminis ra ion of endo oxin o en erally fed subjec s resul ed in a ransien ac iva ion of he coagula ion sys em, as reflec ed by an increase in he plasma concen ra ions of TAT complexes peaking af er 4 h (34.9 ± 4.0 ng/mL, P < .001) (figure 1). Paren eral nu ri ion per se did no influence the plasma levels of TAT complexes in he week prior o endo oxin adminis ra- ion (da a no shown). However, paren erally fed volun eers showed a significan ly more pronounced ac iva ion of he coag- ula ion sys em af er endo oxin injec ion, wi h levels of TAT complexes reaching a peak of 59.9 ± 3.8 ng/mL (P < .001 vs. en erally fed subjec s).

Injec ion of endo oxin was associa ed wi h ac iva ion of he fibrinoly ic sys em, as indica ed by increases in he plasma concen ra ions of plasminogen ac iva or ac ivi y, PA, and PAI-1 (all P < .001 vs. baseline) (figure 2). Paren eral nu ri ion per se did no influence fibrinolysis indexes in plasma in he

**Figure 1.** Ac iva ion of coagula ion. Mean (±SE) plasma concen ra ions of hrombin-an i hrombin III (TAT) complexes af er in ravenous injec ion of endo oxin (2 ng/kg) a t = 0 in heal hy humans who had received n al paren eral nu ri ion (TPN, n = 7) or normal en eral feeding (EN, n = 8) in week before endo oxin adminis ra ion. *P < .05 vs. en erally fed humans by analysis of variance and Newman-Keuls es.

**Figure 2.** Ac iva ion of fibrinolysis. Mean (±SE) plasma concen ra ions of plasminogen ac iva or (PA) ac ivi y, issue ype plasmino- gen ac iva or ( PA), and plasminogen ac iva or inhibi or ype 1 (PAI-1) af er in ravenous injec ion of endo oxin (2 ng/kg) a t = 0 in heal hy humans who had received n al paren eral nu ri ion (TPN, n = 7) or normal en eral feeding (n = 8, EN, closed circles) in week before endo oxin adminis ra ion.
week before endotoxin administration (da a no shown). Further, ac i a ion of he fibrinolytic ic sysem during endotoxemia was no influenced by an ecdn paren eral nu ri ion, compared wi h eneral feeding (figure 2).

Discussion

Cenral venous hrombosis and bical erial infecion are he mos frequen complicaions of paren eral nu ri ion. We hypothesized ba bical erial infecion during paren eral nu ri ion mig result in synergic ic coagulaion ac i a ion via a combined effec of bac eria and pareneral nu ri ion solu ions on he expression of issue fac or, a media or cri ical for fibrin generaion during sepsis [7–9]. We utilized he human model of low-grade endo oxemia as a paradigm for bac erial erial infecion, a model previously shown o induce ac i a ion of bo h coagulaion and fibrinolysis [11–13]. Al hough paren eral nu ri ion did no influence serial plasma indices for ac i a ion of he coagulaion sysem and fibrinolytic ic sysem over 1 week, an ecdn paren eral nu ri ion did enhance endo inxduced coagulaion ac i a ion. Of impor ance, he fibrinolyic ic ac i a ion response remained similar among orally or paren erally fed subjecs. Hence, he effec of pareneral nu ri ion was an enhanced endo oxemia toward fibrin generaion during endo oxemia. The pro hrombic ic s a e was fur her reffec ed by he fac ha several hours af er endo oxin adminis raion, ac i a ion of coagulaion ic s ill proceeded, while fibrinolysis was compely offse .

We consider i unlikely ha he presence of an in venous ca he er, ra her han a 7-day period of bowel res, caused he enhancement of endo oxin-induced coagulaion ac i a ion. In deed, i has been document ed ha prolonged bowel res has an amplifying effec on he meabolic and sysemic response o endotoxin, leading o enhanced e-phae pro eion produc ion, increased coun erregula ory hormone, splanchnic cy okine releas e, and increased neu rophih ac i y [14, 15]. In accorance, o al paren eral nu ri ion was associa ed in pa ien s wi h an exagerrada acu e-phae pro eion response compared wi h he response in en erally fed pa ien s [15]. Our sudy adds o he previousl y published da a ha bowel res is associa ed wi h an enhanced procoagulaion response o endo oxin.

In he presen sudy, lipids were no u ilized as a compoen of he paren eral nu ri ion regimen. Since we recea ly demon- 
s ra ed ha infusion of lipid emulsion in o endo oxemic volun-
ers also selec ively po en ia es coagulaion ac i a ion wi h hou influencing fibrinolysis [13], he shift oward hrombogenesis may be even more pronounced in pa ien s on paren eral nu ri ion wi h lipids. We propose ha , in pa ien s wi h bac erial infecion receiving pareneral nu ri ion, selec ive and synergic ic s imula ion of coagulaion ion may con ribu e o he occurrence of venous hrombosis. These findings may have relevance for he selec ion of pa ien s wi h pareneral nu ri ion who are likely o benefi mos from heparin prophylaxis.

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