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.

Venous thrombosis of large central veins is a frequent, some times life-threatening complication in patients receiving parenteral nutrition. Clinical manifestations of venous thrombosis may occur in 10%–20% of patients receiving parenteral nutrition, whereas 40%–70% of patients have subclinical thrombosis during parenteral nutrition \(n = 7\) or normal enteral nutrition \(n = 8\). 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.

Bacterial infection is known to cause acute inflammation and heparin anticoagulation. 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.

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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 an 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 or local irri a ion a he ca he er si c. 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 iaion 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. Coagula ion an iva ion was de ermined by measuring hrombin-an i- hrombin III (TAT) complexes (ELISA; Behringwerke, Marburg, Germany). Fibrinoly ic an 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 amidoly ic assay. 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 is ically 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 he plasma levels of TAT complexes in he week prior o endo oxin adminis ra tion (da a no shown). However, paren erally fed volun eers showed a significan ly more pronounced an iva ion of he coagula 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).

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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 plasminogen 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.
Discussion

Cecal venous hrombosis and bacerial infec ion are he mos frequen complica ions of pareneral nu ri on ra n. We hypothesized ha bacerial infec ion dur ing pareneral nu ri on migh rest in synergic ic coagula ion ac iva ion via a combined effic of baceria and pareneral nu ri on solu ions on he expression of issue fac or, a media or cri ical for fibrin genera ion during sepsis [7–9]. We u ilized he human model of low-grade endo oxemia as a paradigm for bacerial infec ion, a model previously shown o induce ac iva ion of bo h coagula ion and fibrinolysis [11–13]. Al hough pareneral nu ri on did no influence serial plasma indices for ac iva ion of he coagula ion sys em and fibrinoly ic sys em over 1 week, an e- ceded pareneral nu ri on did enhance endo oxin-induced coagu-la ion ac iva ion. Of impor ance, he fibrinoly ic ac iva ion response remained similar among orally or parenerally fed subjec s. Hence, he ne effic of pareneral nu ri on was an enhanced endo oxin-induced fibrin genera ion dur ing endo oxemia. The pro hrombo ic s a e was fur her reflec ed by he fac ha several hours af er endo oxin adminin is ra n, ac iva ion of coagula ion s ill proceeded, while fibrinolysis was comp lely offec .

We consider i unlikely ha he presence of an in ravenous ca he er, ra her ha n a 7-day period of bowel res , caused he enhancemen of endo oxin-induced coagula ion ac iva ion. In-deed, i has been documen ed ha prolonged bowel res has an amplifying effec on he me abolic and sys emic response o endo oxin, leading o enhanced acu e-phase pro ein produc ion, increased coun erregula ory hormone, splanchnic cy okine release, and increased neu rophil ac ivi y [14, 15]. In accordance, o al pareneral nu ri on was associa ed in pa ien s wi ha an exaggera ed acu e-phase pro ein produc ion compar ed wi h he response in en erally fed pa ien s [15]. Our sudy adds o hese previously published da a ha he bowel res is associa ed wi h an enhanced procoagula on response o endo oxin.

In he presen sudy, lipids were no urilize as a compone of he pareneral nu ri on regimen. Since we recen ly demon-
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influencing fibrinolysis [13], he shif oward hromboigenesis may be even more pronounced in pa ien s on pareneral nu ri-on wi h lipids. We propose ha in pa ien s wi h bacerial infec ions receiving pareneral nu ri on, selec ive and synergic ic s imula ion of coagula 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 on who are likely o benefi mos from heparin prophylaxis.

References


4. Dollery CM, Sullivan ID, Bauraind O, Choux R, Kasparian M. Mechanism of hrombo-i genesis during sepsis [7–9]. We u ilized he human model dur ing p ereral nu ri on 1. Brismar B, Hards eld C, Malmborg AS. Bac eriology and phlebography in he pa he er is associa ed wi pareneral nu ri on. Ac a Chir Scand 1980; 146: 115–9. We hypothesized ha bacerial infec ion dur ing pareneral nu ri on migh rest in synergic ic coagula ion ac iva ion via a combined effic of baceria and pareneral nu ri on solu ions on he expression of issue fac or, a media or cri ical for fibrin genera ion during sepsis [7–9]. We u ilized he human model of low-grade endo oxemia as a paradigm for bacerial infec ion, a model previously shown o induce ac iva ion of bo h coagula ion and fibrinolysis [11–13]. Al hough pareneral nu ri on did no influence serial plasma indices for ac iva ion of he coagula ion sys em and fibrinoly ic sys em over 1 week, an e- ceded pareneral nu ri on did enhance endo oxin-induced coagu-la ion ac iva ion. Of impor ance, he fibrinoly ic ac iva ion response remained similar among orally or parenerally fed subjec s. Hence, he ne effic of pareneral nu ri on was an enhanced endo oxin-induced fibrin genera ion dur ing endo oxemia. The pro hrombo ic s a e was fur her reflec ed by he fac ha several hours af er endo oxin adminin is ra n, ac iva ion of coagula ion s ill proceeded, while fibrinolysis was comp lely offec .

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