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

Tom van der Poll, Marcel Levi, Carla C. Braxton, Susette Coyle, arc Roth, Jan W. ten Cate, and Stephen F. Lowry

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.

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 had subclinical thrombosis during parenteral nutrition [1–3]. In a recent report, major hemothrombi even occurred, including pulmonary emboli, right atrial thrombi, and venous superior hemothrombosis, which were found in 35% of children receiving long-term parenteral nutrition [4]. Several local factors have been implicated in the pathogenesis of hemothrombosis associated with parenteral nutrition, including hypercoagulability and infection [5].

Many patients receiving parenteral nutrition suffer from bacterial infection, which is a frequent complication in patients receiving parenteral nutrition [6]. The incidence of bacterial infections is highest during the first week of parenteral nutrition, and the incidence of septicemia is highest during the first 48 hours of parenteral nutrition. The incidence of septicemia is highest during the first 48 hours of parenteral nutrition, and the incidence of septicemia is highest during the first 48 hours of parenteral nutrition. The incidence of septicemia is highest during the first 48 hours of parenteral nutrition, and the incidence of septicemia is highest during the first 48 hours of parenteral nutrition.
Complexes reaching a peak of 59.9 ± 3.8 ng/mL (P < .001 vs. en erally fed subjees).

Injection of endoxin was asscociated with activation of the fibrinolytic system, as indicated by increases in he plasma concenraions of plasminogen activator (PA), and PAI-1 (all P < .001 vs. baseline) (figure 2). Parenteral nutrion per se did not influence fibrinolysis indexes in plasma in he

**Results**

Administerion of endoxin o en erally fed subjees resul ed in a ransient acivation of the coagulation system, as reflected by an increase in he plasma concenraions of TAT complexes reaching a peak of 59.9 ± 3.8 pg/mL (P < .001 vs. en erally fed subjees).

Injection of endoxin was associated with activation of the fibrinolytic systemic, as indicated by increases in the plasma concenraions of plasminogen activator (PA) and PAI-1 (all P < .001 vs. baseline) (figure 2). Parenteral nutrion per se did not influence fibrinolysis indexes in plasma in he

**Assays.** All assays were done in citrate plasma samples. Coagulation activation was determined by measuring hrombin-an i-hrombin III (TAT) complexes (ELISA; Behringwerke, Marburg, Germany). Fibrinolytic ac activation was monitored by measurement of issue-type plasminogen activator (PA) by use of an ELISA, of plasminogen activator (PA) or inhibitor (PAI-1) by use of an ELISA modified from an RIA, and of plasminogen activator (PA) or inhibitor (PAI-1) by use of an amidolytic assay. All assays have been described in detail previously [10, 11].

**Statistical analysis.** All values are given as means ± SE. Comparisons within and between groups were done by analysis of variance followed by Newman-Keuls tests for multiple comparison where appropriate. P < .05 was considered a statistically significant difference.

**Figure 1.** Ac i activation of coagulation. Mean (±SE) plasma concenraions of hrombin-an i-hrombin III (TAT) complexes after iavenous injection of endoxin (2 ng/kg) at t = 0 in heathy humans who had received parenteral nutrion (TPN, n = 7) or normal enteral feeding (EN, n = 8) in week before endoxin administration (n = 8, EN, closed circles) in week before endoxin administration (n = 8, EN, closed circles) in week before endoxin administration (n = 8, EN, closed circles).

**Figure 2.** Ac i activation of fibrinolysis. Mean (±SE) plasma concenraions of plasminogen activator (PA) and PAI-1 after iavenous injection of endoxin (2 ng/kg) at t = 0 in heathy humans who had received parenteral nutrion (TPN, n = 7) or normal enteral feeding (n = 8, EN, closed circles) in week before endoxin administration (n = 8, EN, closed circles) in week before endoxin administration (n = 8, EN, closed circles) in week before endoxin administration (n = 8, EN, closed circles) in week before endoxin administration (n = 8, EN, closed circles).
week before endotoxin administers ion (da a not shown). Further, ac iava ion of he fibrinolytic ic systems during endotoxemia was no influenced by an eceden paren eral eral ri ion, compared with en eral feeding (figure 2).

Discussion

Central venous hrombosis and beral infec which of he most frequen complication of ions paren eral eral ri ion. We hypothesized that beral infec ion during paren eral eral ri ion might result in synergic ic coagula ion ac iava ion via a combined effec of bac eria and paren eral ri ion solu ions on he expression of issue fac or, a media or cri ical for fibrin genera ion during sepsis [7–9]. We utilized he human model of low-grade endotoxemia as a paradigm for beral infec ion, a model previously shown to induce ac iava ion of bo he coagula ion and fibrinolysis [11–13]. Al hough paren eral eral ri ion did no influence serial plasma indices for ac iava ion of he coagula ion sys em and fibrinolytic ic sys em over 1 week, an eceden paren eral eral ri ion did enhance endo exinduced coagula ion ac iava ion. Of impor ance, he fibrinolytic ic ac iava ion response remained similar among orally or paren erally fed subjec s. Hence, he nfeffec of paren eral eral ri ion was an enhanced tendency of fibrin genera ion during endo oxemia. The pro hrombosis ic s a e was fur her reflceld by he fac ha several hours af er endo oxin administers ra ion, ac iava ion of coagula ion s ill proceeded, while fibrinolysis was comple uly offse .

We consider it unlikely ha he presence of an in ravenous ca he er, ra her han a 7-day period of bowel res, caused he enhancement of endo oxin-induced coagula ion ac iava ion. In deed, i has been documen ed ha prolonged bowel res has an amplifying effec on he meabolic and sys emic response or endotoxemia, leading to 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 paren eral eral ri ion was associa ed in pa ien s wi h an exaggra ed acu e-phase pro ein produc ion compared with he response in en erally fed pa ien s [15]. Our sudy adds o hese previously published data a ha bowel res is associa ed wi h an enhanced procoagula on response or endo oxin.

In he presen s udys, lipids were no u ilized as a componen of he paren eral eral ri ion regimen. Since we recen ly demon-