Parenteral nutrition facilitates activation of coagulation but not of fibrinolysis during human endotoxemia

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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.

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 without infection, whereas 40%–70% of patients receiving parenteral nutrition had subclinical thrombosis during parenteral nutrition without infection as demons trated by venous phlebography [1–3]. In a recent report, major hemothromboplasty, right heart, and vena cava superior thrombosis, were found in 35% of children receiving long-term parenteral nutrition [4]. Several local factors have been implicated in the pathogenesis of thrombosis associated with parenteral nutrition, including hypercoagulability and fibrin deposition on the surface of the endocardium [5].

Many patients receiving parenteral nutrition suffer from bacterial infec tion arising either in conjunction with the venous catheter or in association with the catheterization site. This led us to hypothesize that heparin and other antithrombotic agents do not prevent the occurrence of thrombosis and infec tion during long-term use of parenteral nutrition. A recent study has been performed in a canine model of thrombosis and infec tion [6].

Bacterial infec tion is known to cause acute infection of the coagulation system. In a recent report, major thromboembolic events, including pulmonary embolism, right heart involvement, and vena cava superior thrombosis, were found in 35% of children receiving long-term parenteral nutrition [4]. Several local factors have been implicated in the pathogenesis of thrombosis associated with parenteral nutrition, including hypercoagulability and fibrin deposition on the surface of the endocardium [5].

Materials and Methods

Study design. Fifteen male subjects (mean age ± SE, 28 ± 1 year) were admitted to the Adul Clinical Research Center of the New York Hospital–Cornell University Medical Center after undergoing physical examination and laboratory tests. Informed consent was obtained from all patients before enrollment. The study was approved by the Institutional Review Board of Cornell University Medical College and the University of New York Hospital–Cornell University Medical Center.

Parenteral nutrition was associated with a selectively enhanced activation of the clotting 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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Intravenous injection of endotoxin was associated with activation of the fibrinolytic system, as indicated by increases in plasma concentrations of plasminogen activator (PA), and PAI-1 (all \( P < .001 \) vs. baseline) (figure 2). Parenteral nutrition per se did not influence fibrinolysis indexes in plasma in healthy humans who had received total parenteral nutrition (TPN, \( n = 7 \)) or normal enteral feeding (EN, \( n = 8 \)) in week before endotoxin administration. * \( P < .05 \) vs. en erally fed humans by analysis of variance and Newman-Keuls test.

Assays. All assays were done in citrated plasma samples. Coagulation activation was determined by measuring thrombin-antithrombin III (TAT) complexes (ELISA; Behringwerke, Marburg, Germany). Fibrinolysis was measured by use of an ELISA, of plasminogen activator (PA) by use of an ELISA, and of plasminogen activator inhibitor type 1 (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.

**Results**

Administering endotoxin to enterally fed subjects resulted in a transient increase in plasma coagulation activity, as reflected by an increase in free plasma coagulation activity of TAT complexes peaking after 4 h (34.9 ± 4.0 ng/mL, \( P < .001 \)) (figure 1). Parenteral nutrition per se did not influence plasma levels of TAT complexes in the week prior to endotoxin administration (data not shown). However, parenterally fed volunteers showed a significantly more pronounced increase in coagulation activity of the control subjects after endotoxin injection, with levels of TAT complexes reaching a peak of 59.9 ± 3.8 ng/mL (\( P < .001 \) vs. enterally fed subjects).

Intravenous injection of endotoxin was associated with an increase in the plasma concentration of thrombo-activator complex (TAT) complexes reaching a peak of 59.9 ± 3.8 ng/mL (\( P < .001 \) vs. enterally fed subjects).
week before endotoxin administration on their response. Further, ac cation of he fibrinolytic system during endotoxia was not influenced by an occlusion of parenteral nutrition on their response compared with eneral feeding (figure 2).

Discussion

Central venous thrombosis and parenteral nutrition are all frequent complications of parenteral nutrition. We hypothesized that endotoxin during parenteral nutrition might result in synergistic coagulation and enhanced endotoxin-induced coagu-lation. We utilized the human model of low-grade endotoxia as a paradigm for parenteral endotoxin infusion, a model previously shown to induce ac cation of bovine coagulation and fibrinolysis [11–13]. Though parenteral nutrition on their response did not influence the plasma indices for ac cation of coagulation, the presence of enhanced endotoxin-induced coagulation and fibrinolysis was not significant. In the current study, parenteral nutrition was used as a control to assess the effects of endotoxin on coagulation and fibrinolysis in our model.

We consider it unlikely that the presence of an in vivo model of endotoxin is a prerequisite for parenteral nutrition. Indeed, in vitro models of endotoxin have been used to study the effects of parenteral nutrition on coagulation and fibrinolysis.

References

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