Inhibition of Factor XII in Septic Baboons Attenuates the Activation of Complement and Fibrinolytic Systems and Reduces the Release of Interleukin-6 and Neutrophil Elastase


In previous studies, we have shown that administration of monoclonal antibody (MoAb) C6B7 against human factor XII to baboons challenged with a lethal dose of *Escherichia coli* abrogates activation of the contact system and modulates secondary hypotension. To evaluate the contribution of activated contact proteases to the appearance of other inflammatory mediators in this experimental model of sepsis, we studied the effect of administration of MoAb C6B7 on activation of complement and fibrinolytic cascades, stimulation of neutrophil degranulation, and release of the proinflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Activation of the complement system, as reflected by circulating C3b/c and C4b/c levels, was significantly reduced in five animals that had received MoAb C6B7 before a lethal dose of *E coli* as compared with five control animals that had been given a lethal challenge only. Inhibition of contact activation also modulated the fibrinolytic response, since the release of tissue-type plasminogen activator (t-PA) and the appearance of plasminogen-α2-antiplasmin (PAP) complexes into the circulation was significantly attenuated upon pretreatment with anti-factor XII MoAb. In contrast, plasma levels of plasminogen activator inhibitor (PAI) were modestly enhanced in the treatment group. Deactivation of neutrophils, as assessed by circulating elastase-α-protease inhibitor complexes, and release of IL-6 but not of TNF-α was decreased in anti-factor XII–treated animals. Observed differences in the inflammatory response between treatment and control groups were not likely due to different challenges, since the number of *E coli* that had been infused, as well as circulating levels of endotoxin after the challenge, were similar for both groups. These data suggest that activation of the contact system modulates directly or indirectly various mediator systems involved in the inflammatory response during severe sepsis in nonhuman primates.

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The contact system of coagulation consists of the zyngogens factor XII (Hageman factor), prekallikrein, factor XI, and the substrate procofactor, high–molecular–weight kininogen.1 Biologic sequelae of activation of the initiating protein factor XII of this system include the conversion of prekallikrein to kallikrein,2,3 which can release the vasoactive nonapeptide, bradykinin, from high–molecular–weight kininogen, and the generation of factor XIIa, which can trigger coagulation.4 Several agents can activate the contact system, including bacterial products like endotoxin.5 Therefore, the contact system has been studied intensively with regard to its role in the pathogenesis of sepsis. Several studies have demonstrated that plasma levels of contact system proteins are low in patients with sepsis,6 especially those with shock,4 and correlate with mean arterial pressure.6,11 It has therefore been postulated that hypotension in sepsis, at least in part, is due to the release of bradykinin, which is a potent endogenous vasodilator both through its direct action on smooth muscle and through stimulation of endothelial cells to generate nitric oxide (endothelial-derived relaxing factor)12 and prostacyclin.13 Further support for a role of the contact system in hypotension during the development of sepsis was provided by Pixley et al.,14 who not only demonstrated in a lethal baboon model of sepsis that a protracted decline in blood pressure correlated with activation of the contact system,14 but also that irreversible hypotension was abrogated when animals were pretreated with a monoclonal antibody (MoAb) that inhibits the activity of factor XII.15 Interestingly, this intervention did not affect the development of disseminated intravascular coagulation, suggesting that generation of factor XIIa via activation of factor XII does not contribute to the coagulant stimulus in this sepsis model. Numerous studies have shown that in addition to the contact system, many other endogenous inflammatory mediators are involved in the pathogenesis of sepsis. These mediators include cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-8,16 the plasma cascade systems, such as the complement, coagulation, and fibrinolytic system,17-19 and neutrophils.20,21 Moreover, a number of studies have shown that, at least in vitro, activated contact factors may stimulate the release of IL-1β20 and downregulate Fc receptor expression24 by monocytes, and also activate neutrophils,21 the classic and alternative pathways of complement,26,29 and the fibrinolytic system.30 However, evidence that these interactions also occur in vivo, for example, during development of sepsis, is not available.

In a previous report,15 we have shown that administration of MoAb C6B7, which inhibits activation of factor XII, to baboons that subsequently receive a lethal dose of *Escherichia coli* attenuates contact activation and reduces the secondary decrease in blood pressure in these animals. The

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aim of the present study was to evaluate in sepsis whether activation of factor XII and the contact system may contribute to activation of the complement and fibrinolytic cascades and stimulation of neutrophils and monocytes. For this, we analyzed serial blood samples from these animals using assays reflecting activation of these plasma proteases and blood cells. Our results indicate that inhibition of factor XII by MoAb C6B7 may modulate the inflammatory response during lethal sepsis at various levels.

**MATERIALS AND METHODS**

**Preparation of MoAb C6B7.** The murine MoAb C6B7 (IgG-κ) raised against the light chain of human factor XII fragment (factor XII, β-factor XIIa) was purified from ascitic fluid under sterile conditions as previously described. MoAb C6B7 can inhibit the coagulant activity of factor XII in vitro and retard cleavage of high-molecular-weight kininogen after contact activation of plasma induced by dextran sulfate. In vivo, it modulated the decrease of high-molecular-weight kininogen and inhibited the formation of kallikrein-α₁-macroglobulin complexes, indicating contact system inhibition.

**Induction of sepsis in baboons and pretreatment with MoAb C6B7.** The baboon model of sepsis used in this study has been described in detail elsewhere. Briefly, E coli (organisms) type B were isolated, stored, reconstituted, and characterized as described by Hinstaw et al. A mixed breed of Papio c. cynocephalus/Papio c. anubis baboons was purchased from a breeding colony maintained by the University of Oklahoma Sciences Center Animal Facility at the Oklahoma City Zoo. The animals were transferred to the Oklahoma City Veterans Administration Hospital animal facility, where they were observed for a minimum of 10 days to ensure adequate equilibration before experimentation. A lethal dose of E coli (4 × 10¹⁰ colony-forming units (CFU)/kg body weight) was given as a 2-hour intravenous infusion. Gentamycin was then given as a 9 mg/kg intravenously at 2 hours for 75 minutes, and at 4.5 mg/kg at 6 and 9 hours for 30 minutes. Gentamycin (4.5 mg/kg) was then given intramuscularly at the end of the experiment and twice daily for 3 days to surviving animals. Baboons that recovered from shock were observed daily and medically treated as appropriate. Surviving animals were euthanized after a minimum of 7 days with sodium pentobarbital. In the treatment group consisting of five animals, MoAb C6B7 was infused for 10 to 30 minutes to achieve a plasma concentration of 1 to 2 μmol/L before the lethal challenge with E coli, as previously described. The control group consisted of five animals that received E coli only. The course of the septic process, as well as activation patterns of the coagulation and contact systems in both groups, have been described in detail elsewhere.

Blood samples were obtained from the animals before E coli administration (t = 0) and at 1, 2, 3, 4, and 6 hours thereafter. Samples used for this study were collected in polypropylene tubes on 3.8% wt/vol sodium citrate and stored at −70°C until tests were performed. For the present study, samples from all animals of the treatment group and from four of five animals of the control group were available. We therefore added one lethal baboon to this study, resulting in a control group of five animals. The study protocol used received prior approval by the Institutional Animal Care and Use Committees of the Oklahoma Medical Research Foundation and the Oklahoma Health Sciences Centers, and was performed in adherence to National Institutes of Health guidelines for the use of experimental animals.

**Assays.** C3b/c in baboon plasma was assessed with a radioimmunossay as reported previously. In short, MoAb anti-C3-28, which binds to a neoepitope expressed on human C3b, C3bi, and C3c, was used as a catching antibody, and polyclonal α₂-antithrombin, C3c as detecting antibodies. Results were expressed as a percentage of the amount of C3b/c present in normal baboon serum aged (NBA), i.e., normal baboon serum (NBS) incubated for 7 days at 37°C in the presence of 0.02% (wt/vol) NaN₃.

C4b/c in baboon plasma was assessed with an assay similar to that for C3b/c. In this radioimmunossay, MoAb anti-C4-1, which binds to a neoepitope expressed on human C4b, C4bi, and C4c, was coupled to Sepharose and used as a catching antibody. Polyclonal α₂-antihuman C4 antibodies were used as detecting antibodies. Results were expressed as a percentage of C4b/c generated in NBS by incubation with heat-aggregated IgG (NBS-MAH), according to the method previously described for human serum.

Tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) concentrations were determined using enzyme-linked immunosorbent assays (ELISAs) as reported elsewhere. The lower limits of detection of these assays were 3 and 5 ng/mL, respectively.

Plasminogen activity (PAP) complex levels were determined by an ELISA that had been adapted from a previously described radioimmunossay. Briefly, murine MoAb APR-AP-1, directed against complexed and inactivated α₂-antiplasmin, was coated on microtiter plates. Bound complexes were detected by subsequent incubation with affinity-purified biotinylated polyclonal rabbit antibodies raised against human plasminogen. Levels of PAP complexes were expressed as a percentage of the level present in normal baboon plasma (NBP) in which a maximal amount of PAP complexes had been generated by addition of an equal volume of urokinase (50 μg/mL) in the presence of 0.4 μmol/L mexiteline to inactivate α₂-macroglobulin, further referred to as NBP-MA-UK. The lower limit of detection of this assay was 0.1% of NBP-MA-UK.

Elastase-α₁-protease inhibitor complexes were determined with a radioimmunossay that has been described in detail elsewhere. Results were expressed as nanograms of elastase per milliliter by reference to a standard curve that consisted of NBP to which human neutrophil elastase (Eunos Products Co, Pacific, MO) was added at a final concentration of 2 μg/mL. In this standard, more than 95% of the elastase is complexed to α₁-antitrypsin. The lower limit of detection was 5 ng/mL. Normal values are less than 100 ng/mL.

TNF-α and IL-6 concentrations were measured by ELISA as reported elsewhere. The lower limits of detection were 3.5 and 0.1 ng/mL, respectively.

Plasma endotoxin levels were assayed using a limulus amebocyte lysate assay (Pyrogen; BioWhitaker Inc, Walkersville, MD). The detection limit was 0.05 endotoxin units (EU)/mL. Bacterial viability counts in the inoculum and in freshly collected baboon samples 2 hours after the start of the challenge were determined by standard dilution techniques.

**Statistical analysis.** Values are expressed as the mean ± SEM. Between groups, a nonparametric statistical analysis was performed using Mann-Whitney U/Wilcoxon rank-sum test. A difference was considered significant at P < .05 and highly significant at P < .01 (two tailed).

**RESULTS**

**Complement activation.** Plasma levels of C3b/c and C4b/c were measured to estimate the extent of complement activation in this study. In the control group, a rapid increase of circulating levels of C3b/c was observed during the first 2 hours after the start of E coli infusion (Fig 1A), reaching maximum values of 11.6% ± 0.7% of maximally activated standard baboon serum (NBA). This increase was similar at 1 hour in the treatment group, but became significantly reduced thereafter, reaching peak levels of 6.4% ± 1.3% at 2 hours (Fig 1A). In both groups, C3b/c levels gradually de-
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Fig 1. Complement activation after lethal E coli infusion. Mean ± SEM plasma levels of C3b/c (A) and C4b/c (B) in control (●) and MoAb-treated (○) groups. C3b/c and C4b/c are expressed as a percentage of NBA and NBS-AHG, respectively. Differences between groups, determined by Wilcoxon/Mann-Whitney U test, are significant at *P < .05 and **P < .01.

In both groups, a pronounced increase of PAI-1 levels was observed from 2 hours after onset of the challenge and

at 4 and 6 hours. Concentrations of circulating PAI-1 complexes, which reflect generation of plasmin, the key enzyme of the fibrinolytic system, increased from baseline levels at 1 hour and reached a peak value of 13.2% ± 2.5% of fully activated standard plasma (NBP-MA-UK) at 2 hours (Fig 2B) in control animals. In contrast, in the anti-factor XII-treated group, PAI complexes only moderately increased to a maximum of 6.0% ± 2.0% at 3 hours. PAI levels were significantly different between the groups at 1, 3, and 4 hours. Notably, in this model, a 2-hour infusion of E coli resulted in generation of approximately fivefold more plasmin than observed previously after a lethal bolus injection with E coli, as reported elsewhere.42

In both groups, a pronounced increase of PAI-1 levels was observed from 2 hours after onset of the challenge and
in circulating TNF-α was observed, reaching peak levels of 3,003 ± 506 and 3,372 ± 780 ng/mL at 6 hours in treatment and control animals, respectively (Fig 2C). A significant difference in the course of PAI-1 levels between groups was noted at 3 hours (P < .05), consistent with a decreased consumption of PAI-1 by t-PA in C6B7-treated animals.

Neutrophil degranulation. To study the effect of MoAb C6B7 on neutrophil activation in this experimental model of sepsis, elastase-α1-protease inhibitor complexes were assayed in plasma samples from both groups. Figure 3 shows that anti-factor XII treatment reduced the release of elastase. In control animals, elastase complexes increased during the entire observation period, reaching maximum levels of 1,851 ± 382 ng/mL at 6 hours. This increase was less pronounced in the treatment group, in which peak levels of 913 ± 170 ng/mL were measured. The difference between the course of elastase was significant from 2 hours onward.

Plasma levels of TNF-α and IL-6. Plasma levels of TNF-α and IL-6 were assessed in both groups of animals. The course of TNF-α release on lethal challenge was consistent with previous observations and was not affected by MoAb C6B7: in both groups, a transient and comparable increase in circulating TNF-α was observed, reaching peak levels of 35.4 ± 9.2 and 30.8 ± 4.5 ng/mL at 2 hours in control and treatment groups, respectively (not shown). In contrast, anti-factor XII treatment modestly reduced the appearance of IL-6 (Fig 4). In both groups, administration of E coli resulted in a progressive increase of circulating IL-6, with identical kinetics during the first 3 hours. Thereafter, levels tended to be reduced in the treatment group, and were significantly different from control levels at 6 hours (181.3 ± 86.4 vs 429.2 ± 101.6 ng/mL, P < .05).

Observed differences in activation parameters between treatment and control groups potentially might be due to small differences in the number of microorganisms used for the challenge, rather than to the effect of MoAb C6B7. Therefore, we estimated this number, as well as that in blood samples taken 2 hours after the start of infusion in each animal. Table 1 shows that there were no differences between treatment and control groups with respect to the number of CFU in the infusion fluid given to each animal. However, the number of viable bacteria that could be reconstituted from the plasma 2 hours after the challenge was approximately fourfold less in treated compared with control animals. In contrast, endotoxin levels, which reflect the release of lipopolysaccharide (LPS) from circulating bacteria, were not found to be different between the groups (Table 1).

**DISCUSSION**

In a previous study, we have shown that administration of MoAb C6B7, which inhibits activation of factor XII, to baboons that were subsequently challenged with a lethal dose of E coli was able to reduce factor XII activity by 60%, diminish the decrease in high-molecular-weight kininogen, and prevent the formation of kallikrein-α2-macroglobulin complexes, indicating efficient inhibition of the contact sys-

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**Fig 3.** Course of elastase-α1-protease inhibitor complexes (mean ± SEM) in control (○) and MoAb-treated (○) groups after a lethal dose of E coli. Wilcoxon/Mann-Whitney U test, *P < .05.

**Fig 4.** Plasma levels of IL-6 (mean ± SEM) in control (○) and MoAb-treated (○) groups after a lethal dose of E coli. Wilcoxon/Mann-Whitney U test, *P < .05.

**Table 1. Mean ± SEM Number of CFU of E coli in the Infusion Fluid Before Challenge and in Blood Samples Obtained 2 Hours After the Start of Infusion**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anti-Factor XII</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFU (U/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion fluid</td>
<td>4.27 ± .26</td>
<td>4.67 ± 1.40</td>
<td>.754</td>
</tr>
<tr>
<td>2 h (×10⁸)</td>
<td>1.52 ± .29</td>
<td>6.31 ± 2.59</td>
<td>.009*</td>
</tr>
<tr>
<td>Endotoxin (EU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 h</td>
<td>2.74 ± 1.91</td>
<td>.22 ± .05</td>
<td>.246</td>
</tr>
<tr>
<td>1 h</td>
<td>41.36 ± 8.88</td>
<td>25.17 ± 5.20</td>
<td>.297</td>
</tr>
<tr>
<td>2 h</td>
<td>86.14 ± 11.72</td>
<td>74.0 ± 13.40</td>
<td>.466</td>
</tr>
<tr>
<td>3 h</td>
<td>25.26 ± 6.94</td>
<td>15.90 ± 5.10</td>
<td>.297</td>
</tr>
<tr>
<td>6 h</td>
<td>5.91 ± 1.07</td>
<td>3.79 ± .33</td>
<td>.439</td>
</tr>
</tbody>
</table>

Mean ± SEM plasma levels of endotoxin before (t = 0) and at 1, 2, 3, and 6 hours after E coli infusion. Differences between control and MoAb-treated groups were determined by Wilcoxon/Mann-Whitney U test.

*P < .05.
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The aim of the present study was to evaluate whether MoAb C6B7-induced reduction of contact activation influenced activation of complement and fibrinolytic cascades, activation of neutrophils, and induction of cytokines.

Complement activation in sepsis is considered to result mainly from direct activation by bacteria and their products. The initial activation of C3 immediately following E. coli infusion (Fig 1A) supported the idea of a direct activation by circulating organisms. A number of studies have shown that endotoxin and intact bacteria can activate the complement system directly via the alternative pathway. The observation that C4b/c levels also increased rapidly upon infusion of E. coli indicates that at least part of the activation occurred via the classic pathway. In vitro, addition of these E. coli bacteria to NBS also results in activation of C3 and C4, indicating that direct contact of the microorganisms and/or their products with blood may induce complement activation via the classic pathway, presumably via IgG and IgM antibodies. However, levels of C3b/c and C4b/c remained elevated and continued to increase, respectively, after E. coli infusion had been stopped (Fig 1), suggesting involvement of other activating mechanisms of the complement system, as well. A number of in vitro studies have demonstrated interactions between activated contact proteins and complement factors, although evidence that these interactions also occur in vivo has been lacking. For example, factor XII can activate C1 through cleavage of the C1r subcomponent. Also, kallikrein can cleave C1 subcomponents, but this results in destruction rather than activation. However, kallikrein can replace factor D in the alternative pathway to generate a C3 convertase by cleaving factor B, and in rabbits kallikrein can generate C5a from C5. Our data imply that inhibition of the contact system reduced complement activation in this experimental model of sepsis. Our observations do not allow definite conclusions with regard to molecular pathways involved in interactions between activated contact proteins and the complement system in baboons. However, the fact that activation of C4 was diminished in treated animals, even during the later stages of the septic process, supports a mechanism involving factor XII-induced activation of C1.

Low doses of endotoxin or TNF have been shown to induce a procoagulant state in human volunteers, resulting from a sustained activation of coagulation, with a more transient activation of fibrinolysis. Similar changes occur in baboons following lethal or sublethal doses of E. coli. In a previous study, we have shown that pre-treatment of septic baboons with MoAb C6B7 did not influence the occurrence of disseminated intravascular coagulation, indicating that the contact system does not contribute to coagulation in this model. In contrast, we show here that activation of fibrinolysis was significantly diminished in baboons that received MoAb C6B7, indicating that contact activation had contributed to plasmin formation in untreated animals (Fig 2). A number of in vitro interactions between activated contact factors and the fibrinolytic system have been described. For example, factor Xla, factor Xla, and kallikrein are all capable of directly converting plasminogen to plasmin. However, these reactions are weak and, at plasma concentrations, presumably not significant. However, kallikrein can cleave single-chain u-PA to its active form on cellular surfaces and in a plasmatic environment. Additionally, a factor XII-dependent pathway has been described that involves u-PA-like plasminogen activator that has been partly characterized. Activation of the contact system may also enhance fibrinolysis through the effects of bradykinin on the release of t-PA from the vessel wall. This latter effect would explain the lower levels of t-PA in baboons that received MoAb C6B7 as compared with untreated controls. In a previous study, we showed that activation of factor XII on administration of desamino D-arginine vasopressin to humans contributes significantly to the induction of plasminogen activator activity and is independent of the release of t-PA. Moreover, angioedema attacks due to a hereditary deficiency of the main inhibitor of the contact system, Cl-inhibitor, are associated with concomitant contact activation and plasmin generation. Thus, interactions between the contact and the fibrinolytic system in vivo go beyond the release of t-PA by the endothelium. However, the precise nature of these interactions, as well as their role in sepsis, remain to be established.

Purified plasma kallikrein is able to stimulate neutrophil chemotaxis, aggregation, and oxygen consumption. Furthermore, it also induces these cells to release elastase from their azurophilic granules. Activation of neutrophils in vivo can be assessed by measuring plasma levels of elastase–a1-protease inhibitor complexes. Increased levels of these complexes have been found in human sepsis and were associated with a poor outcome. In this study, circulating elastase–a1-protease inhibitor complexes markedly increased upon infusion of a lethal dose of E. coli, which was significantly attenuated by MoAb C6B7 (Fig 3). Although this effect of factor XII blockade may have been mediated indirectly by a decreased liberation of the anaphylatoxins, C3a and C5a, which are potent inducers of neutrophil degranulation in vitro, these data may also reflect a direct agonistic effect of contact proteases on neutrophil activation in this model of sepsis.

Bacterial counts in the infusion fluid used for the challenge were similar for both groups. However, the amount of circulating colony-forming bacteria 2 hours after the start of the infusion was about fourfold less in the treatment group (Table 1). This implies that upon anti–factor XII treatment, E. coli must have been cleared more efficiently from the circulation or were killed more rapidly as compared with the control. We are not aware of studies showing an inhibitory effect of contact proteins on the phagocytosis of bacteria; rather, factor XIa has been shown to downregulate Fcγ II-receptor expression on monocytes. Alternatively, an enhanced clearance of E. coli organisms in the treatment group may have resulted from the hemodynamic effects of inhibition of the contact system, ie, a better perfusion of the organs. However, it should be noted that minor alterations inflicted on the outer membrane of bacteria may result in a lack of colony formation, which need not necessarily reflect bacterial death or clearance. Moreover, in contrast to bacterial counts, endotoxin levels were similar for both groups. Thus, whatever mechanism operated to reduce bacterial
counts more efficiently upon C6B7 treatment, it still resulted in a release of LPS that did not differ from that in untreated control animals. Previous studies in mice have indicated that protection against lethal sepsis is associated with a reduction in serum LPS levels rather than with a reduction in blood bacterial counts. In agreement herewith are observations that in septic patients the presence of biologically active endotoxins is a better harbinger of clinical sepsis than viable bacteria, and correlates with survival. Despite this, our data raised the possibility that some of the observed effects in the treatment group were due to enhanced clearance rates and/or bacterial killing mechanisms rather than to inhibition of effects of activated contact proteins on other mediator systems. However, this explanation is not supported by the kinetics of TNF-α in both groups, since these were comparable. Furthermore, levels of PAI-1 were not decreased, but were even slightly enhanced in C6B7-treated animals, and the initial increase of IL-6 was similar to that in controls. On the other hand, IL-6 levels during the later stages were modestly reduced in the treatment group. However, this latter observation might support a role for contact proteins in the release of cytokines in vivo, as has been observed in vitro for factor XIIa-induced release of IL-1.

The data presented here demonstrate the complexities of the relationships between blood bacterial numbers, circulating LPS, and inflammatory parameters and the difficulty in establishing their relative roles in experimental infection. In a previous study, we have shown that in this lethal baboon model of sepsis, a protracted decrease in arterial pressure could be attenuated by administration of MoAb C6B7. We concluded that this could be attributed, in part, to a diminished release of bradykinin from high molecular weight kininogen. In addition, as we have shown in the present study, administration of MoAb C6B7 also resulted in attenuation of complement activation, and thus in reduced generation of C3a and C5a. These complement activation products may also have contributed to the observed hemodynamic changes. This explanation is supported by a previous study demonstrating that pretreatment with anti-C5a antibodies in a primate model of sepsis results in a similar recovery in mean arterial pressure.

In conclusion, we demonstrated that administration of a neutralizing MoAb against factor XII to baboons suffering from lethal sepsis is accompanied by a decreased activation of complement and fibrinolytic systems and a reduced release of IL-6 and neutrophil elastase. Our findings suggest that in this animal model, activated contact proteins may contribute to the activation of other inflammatory mediators, and once more illustrate the complexity of mechanisms involved in the pathogenesis of sepsis.

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Inhibition of factor XII in septic baboons attenuates the activation of complement and fibrinolytic systems and reduces the release of interleukin-6 and neutrophil elastase

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