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FINAL TECHNICAL REPORT

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TITLE: Office of Naval Research Project,

"Endogenous Anticoagulation During Extracorporeal Perfusion: Mechanisms and Applications"

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PROGRAM MANAGER: Lerner B. Hinshaw

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SPECIFIC TOPIC: Endotoxin Shock in Dogs: Protective Role of Extracorporeal Perfusion.

We have previously reported that dogs developing endogenous anticoagulation during 90 minutes of arteriovenous extracorporeal perfusion are protected from lethal E. coli endotoxin (1). However, when dogs are perfused and given endotoxin simultaneously with the onset of endotoxin administration, survival is not improved. This finding suggested that the blood and/or tissues might have been primed or "set up" by extracorporeal perfusion to afford protection against endotoxin. Also, we observed that extracorporeal perfusion prolonged whole blood clotting times of dogs without significantly depleting platelets and fibrinogen, or producing disseminated intravascular coagulation (2).

Because of these results, we asked the question if changes in the coagulation system of the dog stimulated by extracorporeal perfusion could have accounted for the protection against endotoxin. Since recent studies (3) have demonstrated that infusing dogs with subcoagulant amounts of thrombin induced anticoagulant activities, we reasoned that the production of subcoagulant amounts of thrombin during extracorporeal perfusion without exogenous anticoagulation (1) might not only explain our ability to establish an extracorporeal system without added anticoagulant, but might also account for the protection against endotoxin.

The question we set out to answer during this year of U. S. Navy support was, "Could we reproduce the protection accorded by extracorporeal

perfusion by infusing subcoagulant amounts of thrombin?" If protection against endotoxin was attained would the responses of the coagulant and fibrinolytic systems to thrombin and endotoxin be associated with protection? The past year's work was devoted to ~~answer these~~ questions by evaluating the percent survival and the responses of the coagulant and fibrinolytic systems to thrombin or saline infusion by infusion of lethal concentrations of endotoxin.

Infusions of dogs with thrombin (0.5 u/kg/min) for 90 minutes significantly increased percent survival following infusion of endotoxin (0.06 mg/kg/min) for 30 minutes. Nine of thirteen dogs infused with thrombin survived seven days (permanent survivors), whereas thirteen of fourteen dogs infused with saline died within 36 hours. Those dogs which survived responded immediately to endotoxin with enhanced anticoagulant and fibrinolytic activity as measured by the Xa one-stage and fibrin degradation product assays respectively. Those dogs receiving saline instead of thrombin did not respond with anticoagulant or fibrinolytic activity until the end of the study. We concluded that thrombin in the correct amounts protected dogs from endotoxin and that this protection was associated with an early anticoagulant and fibrinolytic response to endotoxin infusion ~~(4)~~.

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