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RECOVERY FROM ENDOTOXIN SHOCK AFTER EXTRACORPOREAL PERFUSION WI--ETC(U)
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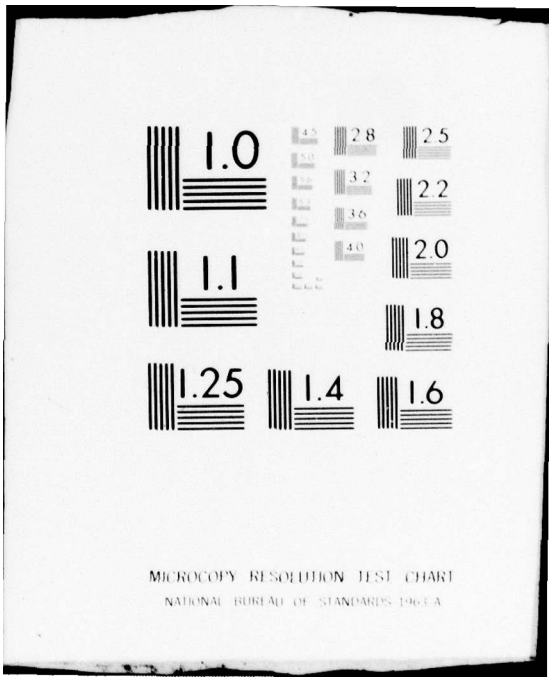
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TECHNICAL REPORT NO. 141

RECOVERY FROM ENDOTOXIN SHOCK AFTER EXTRACORPOREAL PERFUSION WITHOUT ANTICOAGULATION

Beverly Beller-Todd, Linda T. Archer, and Lerner B. Hinshaw

Prepared for Publication

in

Circulatory Shock

University of Oklahoma Health Sciences Center
Departments of Physiology and Biophysics and Surgery
Oklahoma City, Oklahoma

27 December 1979

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ABSTRACT

The purpose of this study was to determine the effect of an extracorporeal nonanticoagulated perfusion system on survival from endotoxin shock in anesthetized closed-chest dogs. Dogs weighing approximately 18 kilograms were perfused 4 hours or served as nonperfused controls. In the perfused animals, blood was diverted from the distal aorta via plastic tubing at 1000 ml/min into a reservoir and returned by means of a roller-type pump to the femoral veins. Whole blood clotting times increased from a control of 7 minutes to greater than 24 hours within 45 minutes of perfusion in the absence of exogenous anticoagulation. After blood became incoagulable, animals were infused with 3 mg/kg E. coli endotoxin during a 30-minute period. Systemic pressures declined during the initial period but returned to baseline values, glucose remained at normal levels and all six dogs thus treated were healthy 7-day survivors. On the other hand, animals infused with endotoxin without extracorporeal perfusion demonstrated hypotension, hypoglycemia, and diarrhea, and five of six dogs died within 36 hours.

KEY WORDS: endotoxin shock, heparin, extracorporeal perfusion, augmented venous return, autoanticoagulation

INTRODUCTION

Excessive bleeding has been reported in clinical practice using heparinized extracorporeal perfusion systems (1-4). Our laboratory has also encountered similar difficulties in animal perfusion studies using heparin (5-7). We recently circumvented this problem by developing arteriovenous and venovenous extracorporeal perfusion systems in dogs without exogenous anticoagulation (8) similar to that of Fletcher et al. (9). Both of our preparations were very stable as demonstrated by relatively constant arterial blood pressure, heart rate, hematocrit, pH and blood glucose concentrations during the course of the perfusions. After 45-60 minutes of the venovenous perfusion at approximately 850 ml of extracorporeal blood flow per minute, arterial whole blood sampled for Lee-White clotting times failed to show any visible sign of coagulation (clotting time >24 hours). Clotting times in the arteriovenous system, extracorporeal blood flow approximately 400 ml per minute, were prolonged (approximately 15 minutes). Animals bled minimally from surgical sites and light microscopy revealed no deleterious perfusion effects, including no fibrin thrombi in heart, lung, liver or kidney tissue in either series.

In the past our heparinized perfusion systems used to study endotoxin shock were limited in time because excessive bleeding and hemodynamic instability resulted in the controls within 2 hours as well as the experimentals (5-7). The recently developed systems (8) without exogenously administered anticoagulation remained stable during the entire observation period (4 or 6 hours), and blood glucose and mean systemic arterial pressures of the dogs showed signs of returning toward control values after endotoxin administration (8). These observations suggested that the perfusion systems offered possible protection and recovery from shock, but experiments were terminated acutely. We conse-

quently designed the present endotoxin shock study utilizing a modification of the perfusion systems to evaluate survival.

METHODS

Twelve adult mongrel dogs of either sex, weighing 17.6±1.2 kg, were anesthetized with intravenous sodium pentobarbital, 25 mg/kg body weight, and divided into two groups. Six animals served as the experimental or perfused group and six served as the control or nonperfused group. Animals were placed on their right sides, loosely secured to the table with gauze bindings on all four limbs, and covered with heating pads to control body temperatures. Experimental preparations were established as follows:

Experimental (perfused) dogs (Figure 1). The right brachial artery of each experimental dog was cannulated to monitor mean systemic arterial pressure and heart rate and for sampling blood. The extracorporeal perfusion circuit consisted of large-bore flexible plastic Tygon tubing and reservoir filled with saline (approximately 500 ml). The proximal ends of the first set of saline-filled tubing (clamped with hemostats to prevent saline loss and blood reflux) were advanced into the distal aorta of each dog via the left and right femoral arteries. The distal ends were placed below the surface of a 400 ml saline-filled plastic reservoir surrounded by a water bath maintained at 40-42°C. A saline-filled line, attached to the bottom of the reservoir, was threaded through a nonocclusive roller-type pump (Medical Specialty Co., Fort Worth, Tex.) and divided into a second set of cannulas which were then surgically inserted into the right and left femoral veins. (These lines were also clamped with hemostats to prevent saline loss and blood reflux.) To initiate the perfusion, all four clamps were simultaneously released, screw clamps on the arterial outflow lines were adjusted to maintain a constant level of blood in the reservoir, and the pump was set at 1000 ml/min.

No animal received an anticoagulant of any kind. All catheters and pressure transducers were maintained with nonheparinized saline. Preperfusion parameters and blood samples were taken just prior to initiation of perfusion and were noted as zero time. Parameters measured periodically during the next 5.5 hours included mean systemic arterial pressure, heart rate, rectal temperature, hematocrit, blood glucose, blood flow, platelet and white blood cell concentrations (8). Modified Lee-White whole blood clotting times were performed at room temperature in disposable glass test tubes.

The design of the present experiment was to administer E. coli endotoxin (Lipopolysaccharide B:055:B5; Difco Laboratories, Detroit, Mich.) if the dog's blood became incoagulable as observed in our previous venovenous study. After 45 minutes, all six perfused dogs had attained that prerequisite. After another 45 minutes, a 30-minute infusion of 3 mg/kg endotoxin was administered to each dog via the tubing leading to the femoral vein. After 4 hours of perfusion, all blood in the extracorporeal circuit was returned to the dog, the femoral arteries and veins ligated, and the cannulas removed. Still under anesthesia, the animals were observed another 1.5 hours and returned to their cages.

Control (nonperfused) dogs. Six dogs served as controls and were treated as much like the experimental animals as possible. One femoral artery and vein of each control dog was cannulated. The artery was used to sample blood and monitor mean systemic arterial pressure and heart rate. The femoral vein was prepared for endotoxin infusion.

After lying on the table for 90 minutes (rather than being perfused for 90 minutes), each control dog was given E. coli endotoxin as previously described for the experimental animals. After a total of 5.5 hours, the cannulas were removed, vessels ligated, and the dogs were returned to their cages.

Since hemoconcentration occurs to a variable degree in dogs subjected to endotoxin shock, animals of both series were given dextran to maintain their hematocrits at control levels. Total mean volumes for the perfused and nonperfused dogs over the entire 5.5 hour period averaged 11±3 cc/kg and 14±2 cc/kg, respectively. Hemoconcentration occurred most often between 30-90 minutes postendotoxin. Gentamicin sulfate, 4 mg/kg, was administered intramuscularly at 2 and 5 hours and daily thereafter since the experiments were not performed aseptically.

Data were analyzed using the student "t" test. Only values of less than 0.05 were considered statistically significant.

RESULTS

All six perfused dogs survived the 3 mg/kg E. coli endotoxin infusion and appeared healthy one week later when sacrificed. Five of six nonperfused dogs given endotoxin, however, died. Four of these dogs died within 24 hours and the fifth died within 36 hours. The surviving dog was sacrificed after 5 days.

The means (±SE) systemic arterial pressure, blood glucose and heart rate of the perfused and nonperfused dogs during the initial 5.5 hour observation period are shown in Figure 2. The mean systemic arterial pressure of the nonperfused dogs initially rose during the 90-minute control period from 131±8 mmHg to 141±6 mmHg, decreased significantly to 110±9 mmHg following the 30-minute endotoxin infusion, and remained low throughout the 5.5 hours of observation. In contrast, the perfused animals began the experiment with a mean systemic arterial pressure of 135±8 mmHg which did not change significantly until after the endotoxin infusion from 2.5 through 4 hours, when the pressures became significantly lower. After

terminating the perfusion, their mean systemic arterial pressure returned to normal, resulting in a significant difference between the two groups at 5 and 5.5 hours.

Blood glucose levels for the nonperfused dogs slowly declined from a zero time value of 112±6 mg/100 ml and reached significantly lower levels (75-43 mg/100 ml) from 4 hours until the end of the observation period. Perfused dogs demonstrated increases in blood glucose levels at 1 and 2 hours (approximately 130 mg/100 ml, $p<0.05$) and significant decreases (88-82 mg/100 ml) at 4 to 5.5 hours, when compared to their initial mean of 113±7 mg/100 ml. The perfused dogs maintained significantly higher blood glucose levels than the nonperfused dogs at 5 and 5.5 hours. Heart rates of each group did not change significantly from their zero time values during the observation period, except that those of the perfused group decreased significantly after termination of perfusion ($p<0.05$). No significant differences in heart rates were observed between the groups.

Body temperature for the control dogs was maintained with heating pads and remained relatively constant, except at the end of the endotoxin infusion when a slight but significant elevation was noted. Despite heating pads, mean temperatures of the perfused group decreased 0.4 to 0.5 degrees during the first hour of extracorporeal perfusion, but returned to preperfusion levels for the rest of the period. Temperatures between the two groups differed insignificantly. Hematocrits were controlled by addition of dextran. Initial mean hematocrit of the perfused dogs was 42% and decreased to 39% following addition of saline in the perfusion circuit. Thereafter it varied between 36 and 39%. There were no significant differences in hematocrit levels between the groups except at 2 hours [controls=46(±2), perfused=38(±2)]. The extracorporeal blood flow rate

for the perfused group was maintained at approximately 1000 ml/min, averaging 51 ml/kg/min.

Table 1 gives the clotting times for the two groups. Mean initial Lee-White whole blood clotting time for the nonperfused dogs was 5.5±0.6 minutes and showed a gradual increase from 1 hour until the end of the experiment, eventually reaching 9.2±0.8 minutes ($p<0.05$). The perfused dogs, on the other hand, had a preperfusion mean clotting time of 7.0±0.4 minutes which progressively rose after the onset of perfusion. The whole blood clotting time tests for each of the six experimental dogs showed that blood did not coagulate from 45 minutes throughout the perfusion. Following cessation of perfusion, clotting time values returned toward normal. A statistically significant difference between the two groups occurred at each measured interval.

Figure 3 demonstrates white blood cell, total neutrophil and platelet counts for the two groups. The bar graphs illustrate that total circulating white blood cell and neutrophil counts were initially similar in both groups and significantly decreased after endotoxin administration. Mean cell concentrations in perfused dogs recovered by 5.5 hours while those in nonperfused animals remained low at that time ($p<0.05$).

Initial platelet counts for both groups averaged 300,000/mm^3. The mean platelet count of the control group dropped slightly with anesthesia and significantly decreased after endotoxin administration, while that of the perfused dogs dropped about 50% in 1.5 hours and decreased slightly after endotoxin administration. Both groups averaged approximately 100,000/mm^3 at 4 and 5.5 hours which was a significant decrease from zero time. There were no significant differences between the groups.

DISCUSSION

This paper describes two important findings: (a) the successful establishment of a high flow arteriovenous extracorporeal perfusion system without exogenous anticoagulation, and (b) the system's amelioration of pathophysiological changes and prevention of death in dogs subjected to endotoxin shock. The perfusion system consisted of an arteriovenous shunt with an air-blood interface at the top of the column of blood in the reservoir and a controlled extracorporeal blood flow of approximately 1000 ml/min. No filters were used in the perfusion circuit. All six dogs developed "autoanticoagulation" following 45 minutes of perfusion and after another 45 minutes were administered endotoxin. The six perfused dogs given endotoxin survived while five of six nonperfused dogs treated likewise died. Although the mechanisms responsible for the recovery of these animals administered endotoxin in the present study are not apparent, data suggest that the following factors were related to survival:

(A) *The extracorporeal system provided hemodynamic support for the shocked animal.* In contrast to the nonperfused dogs, the mean systemic arterial pressure of the perfused dogs fell less drastically after endotoxin infusion, recovered quickly, and returned to the pre-endotoxin level 1 hour after termination of perfusion (3.5 hours following the onset of endotoxin administration). On the other hand, the mean systemic arterial pressure of the control group did not recover but remained depressed for the duration of the experiment. A possible explanation for the maintenance of arterial blood pressure at higher levels in the perfused group after endotoxin is the augmentation of venous return and cardiac output provided by the extracorporeal system and the elicitation of reflex vasoconstriction (10).

(B) *The extracorporeal system provided metabolic support for the shocked dogs.* We consider marked sustained hypoglycemia an indicator of liver damage in canine endotoxin shock. In our earlier work with dogs administered LD_{70} E. coli endotoxin, we found that hypertonic glucose administration for several hours prevented death in all animals (11). However, in recent pilot experiments, we found that glucose administration in LD_{100} endotoxin shock was ineffective since following cessation of glucose administration animals became hypoglycemic and death ensued. We therefore associate liver damage serious enough to prevent hepatic gluconeogenesis with severe endotoxin shock. In the present study, the mean blood glucose concentrations of the perfused animals were higher than those of the controls throughout the experiment and although they fell gradually during the perfusion were maintained within normal limits. The blood glucose of the controls, however, continued to decrease, reaching hypoglycemic values at termination of the study. The fact that the endogenous blood glucose levels of the perfused animals were consistently higher than those of the control dogs suggests the presence of relatively normal hepatic gluconeogenic function in those animals.

(C) *The extracorporeal system provided support for host defense in the shocked dogs.* Studies by Archer et al. in canine endotoxin shock support the view that increased numbers of neutrophils protect liver function and enhance survival (12). Furthermore, recent reports have described beneficial effects of transfused white blood cells as a treatment for septicemia in neutropenic patients (13) and dogs (14). The total circulating leukocyte concentrations of the perfused animals in the present study returned to normal by 5.5 hours and the circulating neutrophil concentrations eventually exceeded pre-endotoxin levels. On the other hand, the leukocyte and neutrophil concentrations of the controls remained very low, showing no evidence of recovery.

These beneficial effects (A, B and C above) due to the extracorporeal system may have been elicited by augmentation of venous return and by prevention of disseminated intravascular coagulation (DIC) in the microcirculation (Figure 4). Bruni et al. (15) demonstrated that an arteriovenous shunt of 313 ml/min increases coronary blood flow following endotoxin administration in dogs, thereby possibly improving myocardial function. Likewise, our present arteriovenous shunt study showing a better maintenance of blood pressure as well as our previous work (8), support the findings of Bruni and others and suggest that the animal is aided by augmenting venous return to the heart during endotoxin shock. However, augmenting venous return cannot explain the beneficial effects with our venovenous perfusion experiments following endotoxin administration (8).

There is considerable information pertaining to abnormal clotting events resulting in or from disseminated intravascular coagulation in dogs administered endotoxin (16-18). Konda et al. (17) have shown that injection of E. coli endotoxin in dogs causes DIC and results in hemorrhagic necrosis of the intestinal mucosa. In the present study, all control (nonperfused) dogs suffered from blood-tinged diarrhea and lost much of their intestinal intimal lining. In contrast, all animals given endotoxin after extracorporeal perfusion-induced "autoanticoagulation" had no diarrhea or loss of intestinal tissue. On this basis, we feel that prevention of DIC in these perfused "autoanticoagulated" dogs is a reasonable hypothesis.

Corrigan et al. administered heparin to 24 of 26 children with septic shock and concluded that the anticoagulant was not influential in increasing survival (19). However, their data indicated that heparin was a useful agent in improving the consumption coagulopathies encountered in their ients. Also, they observed an association between improvement of blood pressure and the abolishment of DIC.

At the present time, we are doing studies to evaluate our "autoanticoagulation" phenomenon. So far, the answer appears complex and will involve much investigation. We feel that the anticoagulation in our system is superior to that of heparin and may eventually lead to advances in the field of anticoagulation therapy. The fact that our perfused dogs survived the endotoxin administration may be the result of the summation of forces of "augmented venous return" and "autoanticoagulation". No one factor may be the whole answer to survival, but many mechanisms may be working in concert. These findings certainly deserve further definitive study and experimental examination.

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TABLE 1

EFFECT OF EXTRACORPOREAL PERFUSION WITHOUT EXOGENOUS ANTICOAGULATION ON CLOTTING TIME

(ENDOTOXIN GIVEN AT 90 MIN; N=6, EACH GROUP)

		Time, hours									
		0	0.5	0.75	1	1.5	2	3	4[a]	5	5.5
NONPERFUSED DOGS	Minutes	5.5	5.5	5.8	6.3	6.5	6.3	7.3	8.2	9.0	9.2
	SE	0.6	0.6	0.6	0.7	0.6	0.6	0.5	0.7	0.7	0.8
PERFUSED DOGS	Minutes	7.2	13.2	∞	∞	∞	∞	∞	∞	44.3	24.8
	SE	0.4	1.2							3.4	2.5

∞ = no visible clotting during 24 hours.

[a]Perfusion discontinued at 4 hours 5 minutes.

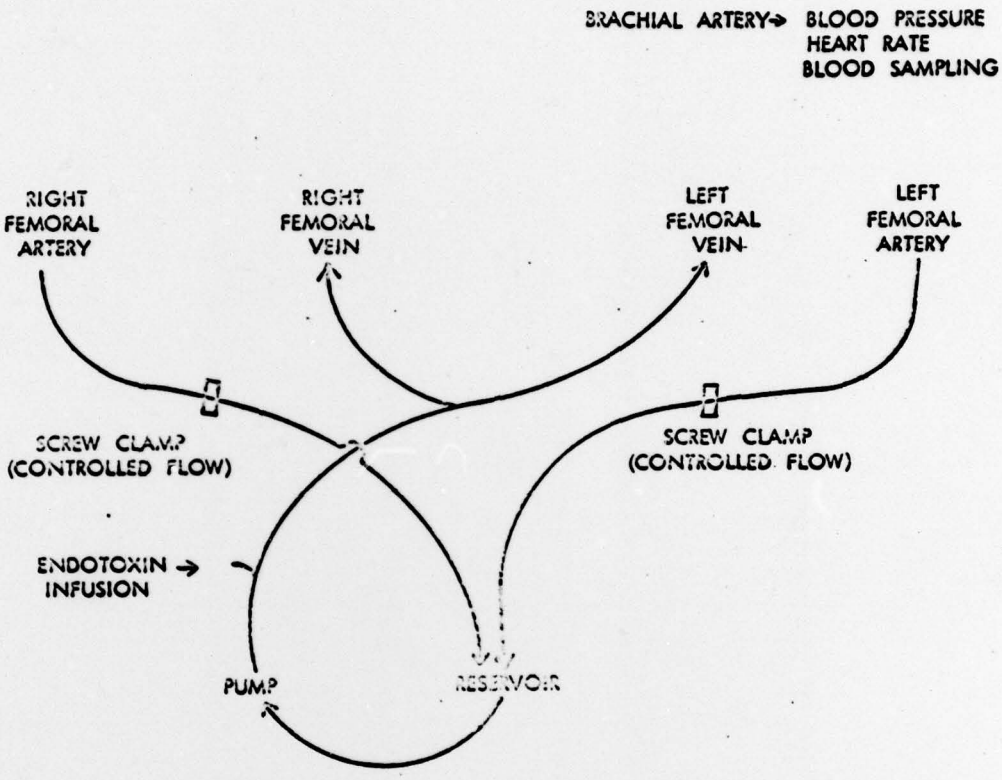

Figure 1. Schematic diagram of perfusion system.

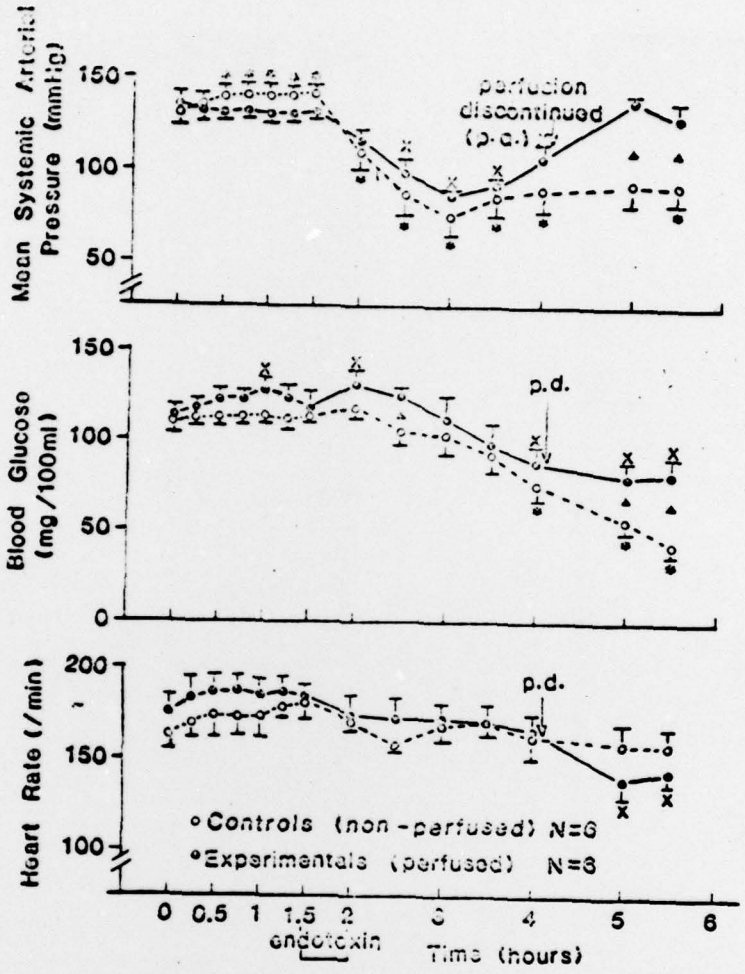

Figure 2. Mean (±SE) mean systemic arterial pressure, blood glucose and heart rate during 5.5 hours of observation.

* = control group, each dog compared to its zero time value, $p<0.05$.

X = experimental group, each dog compared to its zero time value, $p<0.05$.

Δ = experimental group compared to control group, $p<0.05$.

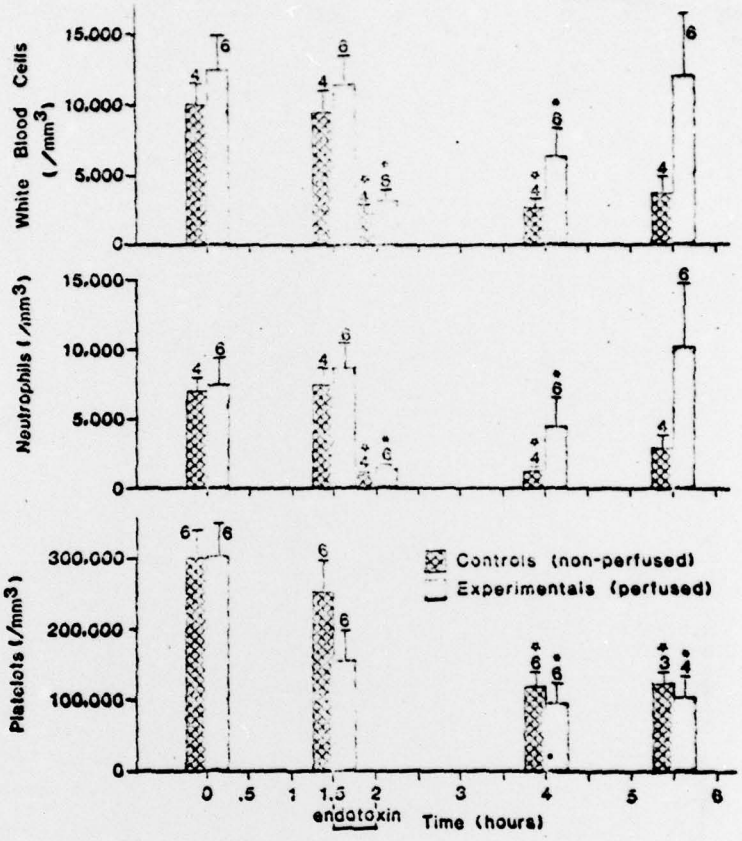

Figure 3. Mean (±SE) white blood cells/mm^3, neutrophils/mm^3, and platelets/mm^3.

☆ = control group, each dog compared to its zero time value, $p<0.05$.

* = experimental group, each dog compared to its zero time value, $p<0.05$.

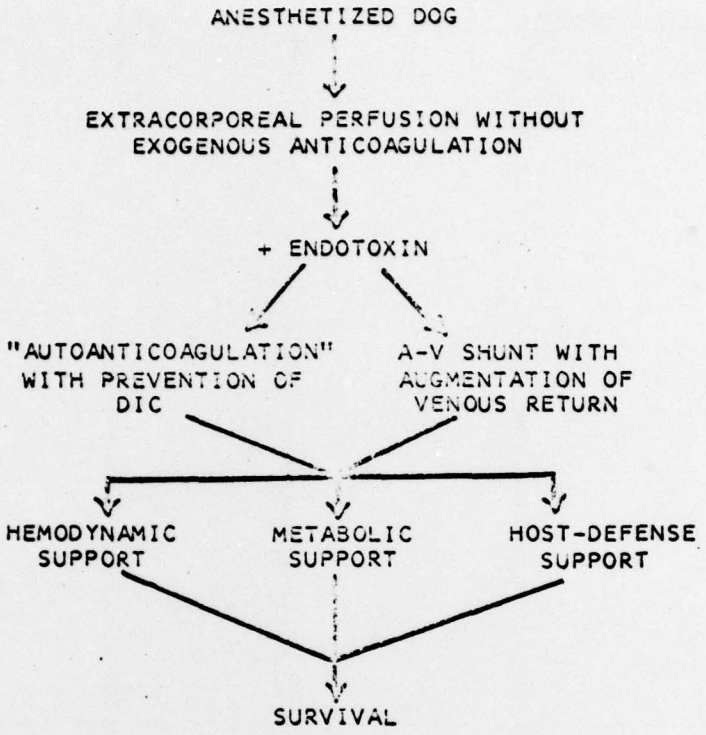

Figure 4. Proposed factors relating to survival following endotoxin administration.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The purpose of this study was to determine the effect of an extracorporeal nonanticoagulated perfusion system on survival from endotoxin shock in anesthetized closed-chest dogs. Dogs weighing approximately 18 kilograms were perfused 4 hr or served as nonperfused controls. In the perfused animals, blood was diverted from the distal aorta via plastic tubing at 1000 ml/min into a reservoir and returned by means of a roller-type pump to the femoral veins. Whole blood clotting times increased from a control of 7 min to

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