
Heparin Pretreatment Suppresses Norepinephrine Concentrations in Dogs in Endotoxic Shock

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Mongrel dogs were treated intravenously with either 1000 units of beef-lung heparin per kilogram of body weight or with isotonic saline, before intravenous administration of E. coli endotoxin. We found significant differences in circulating norepinephrine concentrations between a heparin-pretreatment group (1.89 ± 0.39 µg/liter) and the control group (9.83 ± 4.64 µg/liter), but none with respect to epinephrine. Systolic blood pressures at 360 min were also significantly (P < 0.05) different, 148 ± 8 mmHg as compared with 118 ± 13.4 mmHg. Evidently heparin pretreatment can decrease circulating norepinephrine concentrations in the endotoxic state and changes in circulating catecholamine concentrations can affect physiological variables.

Plasma catecholamine concentrations (1, 2) increase markedly in endotoxic shock. It has been suggested (3) that this plays a major role in physiological responses to endotoxic shock. We wished to determine if suppression of catecholamine release would affect the magnitude of certain physiological responses.

Agents such as steroids and fluids affect certain physiological variables in experimentally induced endotoxic shock (4), but it has not been determined what effect, if any, an alteration in endogenous catecholamine concentrations will have on these same variables. Steroids and fluids are effective secondarily, in that they affect the organism's response after the endotoxic insult. We suggest that a decrease in circulating catecholamines may affect physiological responses directly rather than secondarily.

Methods and Materials

Five control and five preheparinized mongrel dogs weighing 18 to 28 kg were anesthetized with 23 mg of intravenous pentobarbital per kilogram of body weight. A carotid artery and the superior vena cava were cannulated to monitor pressures and pulse rate and for blood sampling. Lactated Ringer's solution, 15 ml/kg body weight, was administered rapidly through a peripheral venipuncture, to expand the circulating volume before endotoxin administration. We allowed 10 min for intravascular equilibration. Systolic, diastolic, and central venous pressures were monitored continuously (E for M. Instruments, Houston, Tex.). Additional variables monitored, intermittently were pulse rate, temperature, respiratory rate, and urine output. To five animals, 1000 units of beef-lung heparin per kilogram was given intravenously and 20 min later, just before endotoxin administration, samples of arterial blood were drawn for use in measuring hematocrit, epinephrine, and norepinephrine (Bio-Science Labs., Van Nuys, Calif). E. coli endotoxin (Difco Labs, Detroit, Mich.), 5 mg/kg body weight, in 10 ml of physiological saline, was then given during 5 min via a peripheral vein. Hematocrit was deter-

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Fig. 1. The arterial total catecholamine, epinephrine, and norepinephrine concentrations after intravenous endotoxin administration in controls and pre-heparinized dogs
Mean ± SEM. Five dogs used at each point

Fig. 2. Arterial systolic pressure as measured by in-dwelling catheter in control and pre-heparinized dogs at intervals indicated after intravenous endotoxin administration
Mean ± SEM. Five dogs used at each point

Results

The heparinized dogs had significantly decreased norepinephrine concentrations in response to the endotoxic insult (Figure 1). One hour after endotoxin administration, control samples averaged, per liter, 11.02 ± 4.6 µg of total catecholamines and 9.83 ± 4.64 µg of norepinephrine, while the heparin pretreated group averaged 2.84 ± 0.63 and 1.89 ± 0.39 µg/liter, respectively (P < 0.001).

Average systolic blood pressure differed between the two groups, even though enough endotoxin was administered to both groups to kill them all within 22 h. The difference in systolic pressures increased as the experiment progressed, so that by 6 h the control group had an average systolic pressure of 118 ± 13.4 mmHg while the preheparinized group had an average systolic blood pressure of 148 ± 5.89 mmHg (P < 0.05) (Figure 2). We saw no differences between the two groups in the other variables monitored.

The mechanism of the heparin/catecholamine interaction is being investigated further.

References