Direct Cardiac Action of *E. coli* Endotoxin (36856)

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Gram-negative septicemia and toxemia are clinically important entities. Although most investigators (1–3) have concluded that any deleterious effect of endotoxin on cardiac dynamics is probably due to initial changes in peripheral circulation, the possibility of primary depression of cardiac functions by the toxin has not been ruled out completely.

The present study was undertaken to evaluate the possibility of direct endotoxin effect on the heart.

Methods. A group of mongrel dogs, weighing 12 to 20 kg each, were anesthetized with sodium pentobarbital (30 mg/kg, iv). The chest was opened by midsternum splitting technique, while the respiration was maintained by a Harvard pump respirator. A cannula was inserted into the aortic arch through an incision made in the left femoral artery, and aortic blood pressure was monitored by a transducer and a Sanborn or Beckman direct-writing oscillograph. The ascending aortic blood flow as measured by a Carolina electromagnetic flowmeter, the probe having been snugly placed around the aorta. The contractile force of the left ventricle was measured by a Walton-Brodie strain gauge sewn to the left ventricular wall. Both vagus nerves were cut.

A metal catheter was inserted into a main branch of the left coronary artery through an incision made on the left carotid artery.

In Group I (14 dogs), *E. coli* endotoxin (0.1 mg/kg of 0111.B4 lipopolysaccharide), dissolved in 1 ml of 5% dextrose in water, obtained from Difco Laboratory, Detroit, was infused into the coronary artery within a 1-min period.

In Group II (9 dogs), 3 mg/kg of reserpine (Serpasil[1]) was given intramuscularly for 3 consecutive days, and then endotoxin in the same amount and manner as indicated for Group I was infused.

In Group III (8 dogs), endotoxin was infused on the third day in the same amount and manner as shown in Group I. These dogs were pretreated with 48/80 (0.2 mg/kg on the first day, and 0.5 mg/kg on the second day, iv) and 200 mg/day, iv, of cortisone acetate (Cortone[2]) for 2 days. The compound 48/80 is a mixture of *p*-methoxy-*n*-methylphenylethylamine moieties, donated by the Burroughs-Wellcome Research Laboratories in Research Triangle of North Carolina, and is known to be one of the powerful histamine-releasing agents.

In Group IV (6 dogs), 0.25 mg/kg of M. J. 1999 (Sotalol; DL-4-(2-isopropylamino-1-hydroxyethyl) methanesulphonanilide), supplied by Mead Johnson Research Center of Evansville, IN, was given intravenously and after 30 min endotoxin as previously indicated was infused. Sotalol is a potent beta-adrenergic receptor blocking agent.

Group V (5 dogs) was subjected to a total right heart–lung bypass procedure. Systemic venous blood returning to the superior and inferior vena cavae after oxygenated in an artificial oxygenator was pumped into the femoral artery. After the pulmonary artery had been ligated, the blood returning to the right ventricle represented the total myocardial blood flow, which was measured by a rotameter. Toxin was infused into the coronary artery while the coronary perfusion pressure and flow rate, as well as heart rate, were held constant.

Results. In Groups I, II and III the aortic

[1] Serpasil is a registered trade name of reserpine, and was obtained through Ciba-Geigy Pharmaceutical Company in Summit, NJ.

[2] Cortone is a registered trade name for cortisone acetate, donated by Merck Sharp & Dohme of West Point, PA.

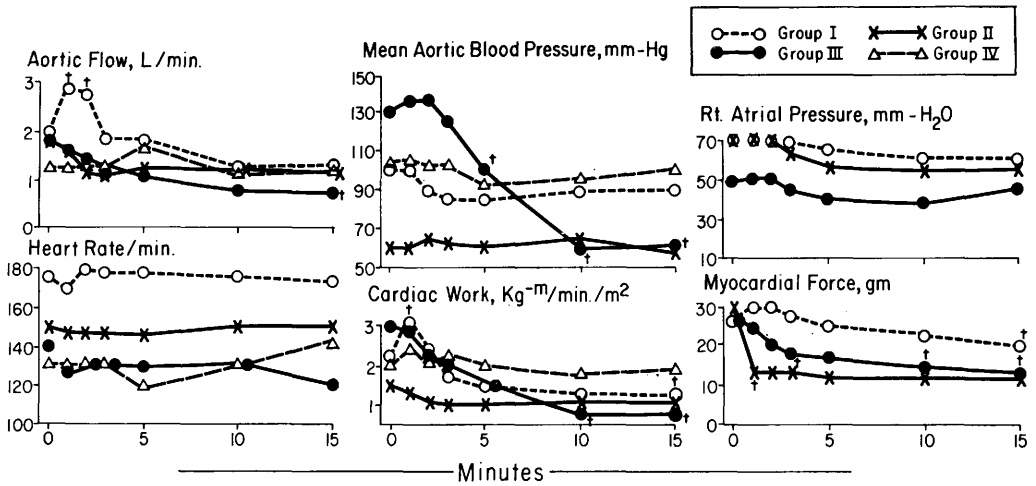

FIG. 1. The mean values of cardiovascular responses following intracoronary arterial infusion of *E. coli* endotoxin (0.1 mg/kg in 1 ml of 5% dextrose in water over 1-min period) in four groups of dogs. Group I (○- - -) the control group; Group II (×—) those dogs pretreated with reserpine; Group III (●—) the group of dogs which have been pretreated with 48/80 and cortisone acetate; Group IV (△- -) the dogs pretreated with Sotalol, a beta-adrenergic receptor blocking agent. († indicates the statistical significance of the observations made against the control value of each experimental group at the level of $p < .05$ or less).

blood flow, myocardial contractile force, left ventricular work, aortic pressure, right atrial pressure and heart rate were measured. In Group I which had received only endotoxin, the aortic flow increased after 1 min and remained high for a period of 3 to 5 min, then declined until the dog died in shock. In Group II, this response was attenuated and the aortic flow decreased immediately. In Group III the aortic flow decreased immediately also. The myocardial force measured after endotoxin (Group I) showed an initial increase within 1 min which leveled off after 5 min. In Group II suppression of the positive inotropic response occurred and in Group III there was complete elimination of the effect. Since endotoxin increased aortic flow and myocardial contractile force, it logically follows that there was a transient corresponding increase in left ventricular work which was eliminated to some extent by reserpine pretreatment (Group II) and totally abolished when dogs were pretreated with the 48/80 and cortisone (Group III). The aortic pressure for all three groups decreased after 5 min when myocardial force reached its low point. The right atrial pressure and rate were minimally affected by endotoxin, and pretreatment did not alter these variables. Figure 1 shows the six variables measured and the responses in Groups I, II and III which are discussed above.

In Group IV the dogs were pretreated with Sotalol, a beta-adrenergic receptor blocker and the initial increases seen in the aortic flow, myocardial work and left ventricular work done when endotoxin was given, were prevented. In Group IV, myocardial force and right atrial pressure were not measured. These results are illustrated in Fig. 1.

In Group V a total right heart–lung bypass with pulmonary artery ligation allowed only myocardial blood to enter the right ventricle. Measurements of this coronary venous flow showed a moderate to significant decrease when endotoxin was infused in four dogs. The coronary venous flow was not changed by infusion of toxin in one dog. The coronary perfusion pressure, cardiac work load and heart rate were all maintained at a constant level. (see Fig. 2).

Discussion. The present study suggested that initial cardiac responses (increased aortic blood flow, myocardial contractile force,

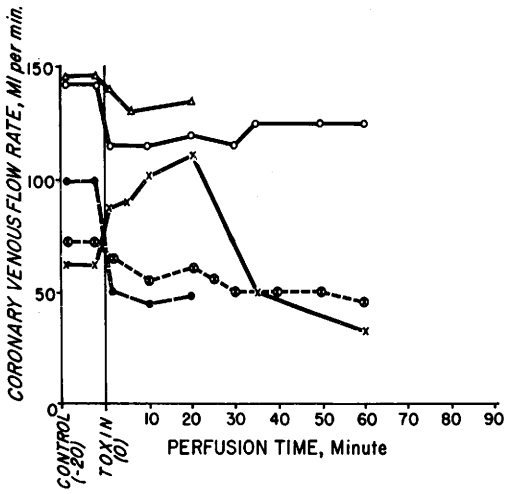

FIG. 2. During total right heart-lung bypass procedures, intracoronary arterial infusion of *E. coli* endotoxin (0.1 mg/kg in 1 ml of 5% dextrose in water over 1-min period) caused coronary arterial vasoconstriction in all but one dog studied. Each line represents the changes of coronary venous flow rate observed in each dog, following infusion of toxin.

and left ventricular work done) may be mediated by catecholamines since depletion of catecholamines by reserpine (Group II) or the blocking of beta-adrenergic receptor sites by Sotalol (Group IV) attenuated these initial responses. We concur with Spink and co-workers' (4) report correlating plasma catecholamine level with hemodynamic changes in canine endotoxin shock.

The results from Group III dogs in which histamine stores were depleted showed an incomplete attenuation of initial cardiac responses, indicating that catecholamines are not the only mediator of endotoxin. The animals who received endotoxin after depletion of histamine were particularly prone to fatal arrhythmias and it can be postualted that histamine together with catecholamines have a role in integration of the heart's electrical as well as mechanical activities.

The present study indicates that endotoxin may directly affect the coronary vessels to cause constriction. This would explain the decrease in coronary venous flow after endotoxin infusion when perfusion pressure, work load and heart rate were maintained at constant levels. This direct effect of endotoxin has been demonstrated on isolated canine saphenous vein strips and on carotid arterial strips by Vick (5).

Summary. *E. coli* endotoxin exerts a direct vasoconstrictor effect on the coronary vessels. *E. coli* endotoxin also causes an initial increase in aortic blood flow, myocardial contractile force, and left ventricular work done. These initial cardiac responses can be attenuated by depleting catecholamines or by blocking beta-adrenergic receptor sites. The initial responses are somewhat modified by depletion of histamine indicating that catecholamines are not the sole mediators for the initial effects of endotoxin.

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