

Effects of Endotoxin on Myocardial Hemodynamics, Performance, and Metabolism During Beta Adrenergic Blockade¹ (35759)

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The question of the precise role of the heart in shock has been largely unresolved (1). Although it is generally agreed that the heart will ultimately fail in shock, its possible contributory role in the development of irreversibility is in serious question. A prevailing view is that the heart is one of the first organs to fail in shock (2-5). Solis and Downing (6) found that ventricular contractile force was diminished after endotoxin even when arterial pressure was maintained. Lefer and others have identified a myocardial depressor substance (MDF) in the plasma of animals in hemorrhagic or endotoxin shock (7-10). They have postulated that this factor may perform an important role in the pathogenesis of irreversibility by depressing excitation-contraction coupling or by impairing the cardiac machinery directly (8). It is a possibility that MDF is a toxic substance gradually released by some ischemic organ or is a normally occurring metabolite which accumulates in the plasma and reaches toxic concentrations (7). On the other hand, Goodyer found that ventricular contractile capacity was enhanced in endotoxin shock as a result of increased sympathetic drive (11), and current studies carried out in this laboratory have failed to demonstrate a direct cardiotoxic influence of endotoxin (12). It is conceivable that a cardiodepressant action of endotoxin could be masked by a simultaneous myocardial stimulating action of catecholamines released as a result of systemic hypotension. The present study was devised to explore this possibility by the utilization of pharmacological doses of a beta adrenergic

blocking agent. Results from the study fail to reveal a myocardial depressant effect following a lethal injection of endotoxin. Cardiac performance was unimpaired after endotoxin in the presence of beta adrenergic blockade.

Materials and Methods. Experiments were carried out on adult mongrel dogs intravenously anesthetized with sodium pentobarbital, 30 mg/kg. The basic procedure was to support an isolated left ventricle by blood exchanged with a heparinized support animal. The donor heart dog was anesthetized, and the chest was opened by median sternotomy after the animal was placed on a constant volume respirator. The azygous vein and subclavian artery were ligated and divided. Ligatures were loosely placed around the thoracic aorta distal to the subclavian artery, the brachiocephalic artery, and superior and inferior vena cavae. The pericardial sac was opened along its ventral surface and the animal was heparinized (3-5 mg/kg). The vagi were then cut in the neck and the brachiocephalic artery was cannulated with a Tygon tube elevated to a height of 100-125 cm above the heart level. The superior vena cava was cannulated with a blood filled plastic tube led through a roller-type blood pump prepared to draw blood from the aorta of the support dog. Blood was allowed to flow through the brachiocephalic cannula and to fill the Tygon tube. The purpose was to provide an adequate hydrostatic pressure for coronary perfusion and to allow the transfer of the heart to the external perfusion system without interruption of coronary flow. The aorta of the isolated heart was then tied distal to the origin of the brachiocephalic artery, the superior vena caval inflow from the pump was commenced at about 120

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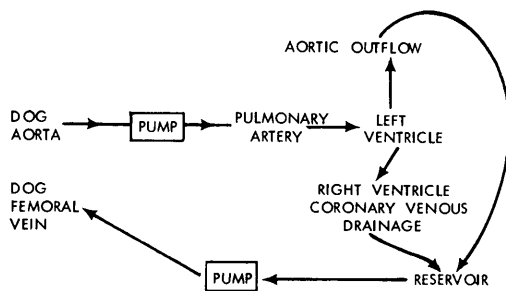


FIG. 1. Schematic diagram of isolated heart preparation.

ml/min, and the inferior vena cava was immediately ligated. Blood from the aortic outflow of the isolated heart was collected in a plastic reservoir (Fig. 1) and returned to the dog at a flow rate equal to the superior vena caval inflow. The heart and lungs were then removed from the chest and supported by the trachea in the external system with adequate coronary pressure and flow constantly provided. The lungs of the isolated heart were not ventilated, and the support animal was respiring spontaneously.

A strain gauge arch was sutured under stretch to the lateral wall of the left ventricle for measurement of myocardial contractile force in some experiments (13). Left ventricular pressure was measured simultaneously for end diastolic pressure (0–40 mm Hg), and systolic pressure (0–200 mm Hg) by means of separate Statham pressure transducers attached by a Y-connector to a plastic cannula inserted through a purse string suture in the apex of the left ventricle.

The right heart was then bypassed after first placing a saline filled plastic tube into the right ventricle via the atrium, and then cannulating the pulmonary artery from a T-connector previously secured to the superior vena caval inflow tubing. The cannulation of the pulmonary artery required only a few seconds during which time the coronary vessels were retrograde-perfused with blood by hydrostatic pressure from the aortic outflow tubing. Coronary venous blood was collected from the right ventricular drain into a plastic reservoir and returned together with brachiocephalic outflow to the support dog via a second pump. Cardiac output was taken as the sum of aortic outflow and coronary

flow, both measured with a cylinder and stop watch. Temperature of coronary venous blood was monitored with a temperature probe. Aortic pressure, left ventricular pressures, cardiac contractility and ECG of the isolated heart, and systemic pressure of the support animal were monitored continuously on a Sanborn recorder. The first derivative of the left ventricular pressure, $dP/dT_{\max}$, was also continuously recorded by means of a resistance-capacitance differentiating network. Mean aortic pressure and cardiac output were increased steadily in the isolated heart preparation by adjustment of a screw clamp on the aortic outflow and elevation of pump speed supplying the pulmonary artery. An Instrumentation Laboratories blood gas analyzer was utilized for coronary arterial and venous pH determinations. Oxygen content of coronary arterial and venous blood was measured by a Van Slyke manometric blood gas analyzer. Simultaneously obtained coronary blood flow measurements permitted the calculation of oxygen uptake and carbon dioxide production from the product of coronary flow and A-V oxygen or carbon dioxide differences.

During the equilibration period of the isolated heart preparation, aortic pressure was stabilized at an average of 107 mm Hg with a cardiac output of 76 ml/min/kg of body weight (based on the wt of the heart donor dog). These pressure and flow values supported and maintained left ventricular systolic and diastolic pressure, coronary blood flow, and myocardial oxygen uptake in the physiological range, and were maintained during the entire experiment by screw clamp adjustment on the left ventricular outflow tubing and by maintaining a constant pulmonary arterial inflow.

Stroke work, in gram · meters, was calculated from the formula used by others (14):

$(\text{MAP} - \text{LVEDP}) (\text{SV}) (1.36)/100$,
where MAP = mean aortic pressure (mm Hg); LVEDP = left ventricular end diastolic pressure (mm Hg) and SV = stroke volume in ml, determined by dividing cardiac output by heart rate. The acceleration component of left ventricular stroke work was disregarded in the calculations on the basis

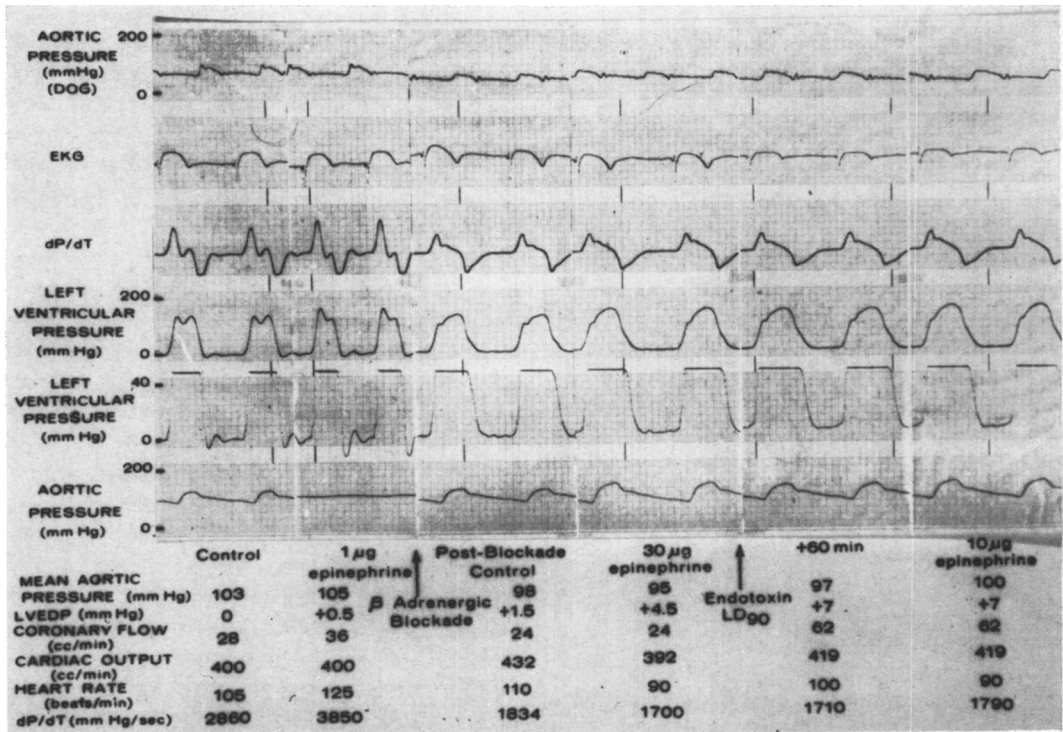


FIG. 2. Effects of β -adrenergic blockade (propranolol, 0.5 mg/kg), before and after endotoxin, on the inotropic, chronotropic, and coronary hemodynamic responses of the isolated heart to injected epinephrine (representative experiment): (lowest frame, second record strip) mean aortic pressure shown.

that it represents less than 1% of total stroke work (15). Cardiac power was calculated and expressed as work per second. The maximum change in pressure ($dP/dT_{\max}$) occurring during isometric contraction of the left ventricle (14, 16) was continuously recorded and expressed as the first derivative of the pressure rise. Calibration of the dP/dT recording was carried out by analysis of the slope of a line drawn tangentially to the steepest portion of the left ventricular isovolumetric tracing and expressed as mm Hg/sec (17). Oxygen uptake was assumed to be negligible in atria and right ventricle (bypassed) as was reported by others (18). Propranolol, 0.5 mg/kg, was infused during a 15-min period in a volume not exceeding 20 ml. The degree of beta adrenergic blocking characteristics was assayed by intracardiac injections of epinephrine or isoproterenol and blockade was essentially complete for chronotropic, inotropic, and coronary vaso-

dilatory responses to injected epinephrine. Blockade was evaluated periodically during the total course of the experiments. At the end of the control period, an LD₉₀ of *E. coli* endotoxin, 1.2 mg/kg (Difco, Detroit), based on the weight of the dog providing the heart, was injected into the pulmonary arterial inflow of the isolated heart. An additional amount of endotoxin based on the weight of the intact table dog was intravenously administered to the support animal. Animals providing the isolated heart averaged 5.5 kg while intact support animals were 20.5 kg in average weight.

Results. Figure 2 illustrates the typical effects, in a single experiment, of beta adrenergic blockade, before and after endotoxin, on the inotropic, chronotropic, and coronary hemodynamic responses of the isolated heart to epinephrine. In general, all experiments demonstrated that a dose of intravenously

TABLE I. Effect of Endotoxin (LD_{50}) on Intact Support Animal Following β -Adrenergic Blockade (mean $\pm$ SE; $N = 6$).

Period	Mean systemic arterial pressure (mm Hg)	Heart rate/min
Control	108 (± 7)	158 (± 8)
Post- β -adrenergic blockade (propranolol, 0.5 mg/kg)	89 (± 11)	123 (± 3)
Postendotoxin (LD_{50})		
20-30 min	59 (± 11)	113 (± 4)
50-75 min	56 (± 5)	130 (± 9)
80-125 min	33 (± 5)	103 (± 7)

administered propranolol of 0.5 mg/kg of body weight was sufficient to produce nearly complete beta adrenergic blockade of the isolated heart. Intracardiac injections of epinephrine or isoproterenol of 0.5 μ g resulted in significant positive inotropic and chronotropic cardiac responses, and increased coronary blood flow, prior to propranolol administration. After beta adrenergic blockade, and during the total course of the present experiments, these three types of cardiac responses were essentially abolished after 10-20 μ g injections of catecholamines.

Table I shows the effect of an LD_{50} injection of endotoxin on the intact support dog, supplying blood to the isolated heart, following beta adrenergic blockade. Mean systemic arterial pressure and heart rate decreased after propranolol injection, and fell significantly lower during a 2-hr period after endotoxin injection.

To assay the effects of endotoxin on myocardial performance and metabolism, it was essential that certain parameters were controlled, and these are shown in Table II. As shown, mean aortic pressure (coronary pressure) and cardiac output of the isolated heart were maintained relatively constant. Coronary blood temperature fell somewhat in spite of artificially imposed warming procedures because of the profound hypothermia developed in the severely shocked support animal. This degree of temperature depression in the perfusion medium of the isolated heart, however, did not appear to exert a significant decremental influence on myocardial metabolism.

Hemodynamic responses of the isolated heart during constant cardiac output and mean coronary perfusion pressure, are illustrated in Table II. Beta adrenergic blockade did not significantly alter coronary blood flow or coronary vascular resistance ($p > 0.10$). Mean flows and resistances, however, were

TABLE II. Effect of Endotoxin (LD_{50}) on Hemodynamics of Isolated Heart Preparation Following β -Adrenergic Blockade (mean $\pm$ SE; $N = 6$).

Period	Mean aortic (coronary) pressure (mm Hg) ^a	Cardiac output (ml/min) ^a	Coronary blood temp	Coronary blood flow (ml/min)	Coronary vascular resistance (mm Hg/ml/min)
Control	107 (± 2)	412 (± 9)	38 (± 0.4)	47 (± 5)	2.4 (± 0.3)
Post- β -adrenergic blockade (propranolol, 0.5 mg/kg)	106 (± 2)	418 (± 11)	38 (± 0.6)	55 (± 10)	2.2 (± 0.4)
Postendotoxin (LD_{50})					
20-30 min	106 (± 2)	411 (± 12)	37 (± 0.4)	77 (± 15)	1.7 (± 0.3)
50-75 min	106 (± 2)	412 (± 7)	37 (± 0.7)	86 (± 12)	1.3 (± 0.1)
80-125 min	107 (± 3)	443 (± 11)	36 (± 0.9)	110 (± 20)	1.0 (± 0.2)

^a Parameters controlled in the experiments.

TABLE III. Effect of Endotoxin (LD_{90}) on Cardiac Performance Following β -Adrenergic Blockade (mean $\pm$ SE; $N = 6$).

Period	Left ventricular end diastolic pressure (mm Hg)	dP/dT (mm Hg/sec)	Stroke work g·m	Heart rate/ min	Power (work/sec)
Control	+3.8 (± 1.4)	2294 (± 233)	4.3 (± 0.4)	143 (± 15)	9.7 (± 0.4)
Post- β - adrenergic blockade (propranolol, 0.5 mg/kg)	+4.5 (± 1.5)	2188 (± 186)	4.9 (± 0.6)	125 (± 15)	9.6 (± 0.3)
Postendotoxin (LD_{90})					
20-30 min	+4.4 (± 1.6)	2230 (± 173)	5.0 (± 0.6)	120 (± 14)	9.4 (± 0.3)
50-75 min	+8.5 (± 4.6)	2202 (± 160)	5.1 (± 0.5)	112 (± 10)	9.1 (± 0.4)
80-125 min	+5.0 (± 0.6)	2248 (± 323)	6.4 (± 0.8)	100 (± 15)	10.3 (± 0.5)

markedly changed after endotoxin injection ($p \leq 0.05$). Coronary blood flow steadily increased to double the control value ($p < 0.05$), 50-125 min postendotoxin, while coronary vascular resistance progressively fell to approximately 50% of the preendotoxin value ($p \leq 0.05$, 50-125 min period).

The effects of an LD_{90} endotoxin on cardiac performance following propranolol are shown in Table III. Left ventricular end diastolic pressure (LVEDP), dP/dT , and cardiac power (work/sec) were unaltered by propranolol administration prior to endotoxin injection. Heart rate reduction resulted in a rise in stroke work since cardiac output, "after load" (aortic pressure) and "preload" (LVEDP) were relatively unchanged. During the 2-hr period after endotoxin, LVEDP, dP/dT , and power remained unchanged while a progressively developing bradycardia from 125 to 100 beats/min resulted in gradually raising stroke work from a mean of 4.9 to 6.4 gram-meters (g·m).

Finally, pH and oxidative metabolic parameters were studied in the isolated heart and results show no significant alteration in oxygen uptake ($p > 0.10$) although a decrease in carbon dioxide production is observed within 1 hr after endotoxin injection (Table IV). Coronary arterial and venous pH are significantly lowered during the entire post-

endotoxin period ($p \leq 0.05$). Propranolol administration exerted no notable effect on pH, oxygen uptake, and carbon dioxide production prior to endotoxin injection.

Figure 3 is a representative experiment demonstrating the absence of a deleterious effect of endotoxin on cardiac hemodynamics, work performance, and metabolism during beta adrenergic blockade.

Discussion. The experimental evaluation of a possible direct detrimental action of endotoxin on the myocardium is a difficult complex problem. Venous return has been demonstrated to fall after endotoxin in both canine and primate species and sufficient information is available to account for the subsequent drop in cardiac output entirely on the basis of peripheral, extracardiac factors (19-22), during the early phase of shock. The present study, a recent report (12), and parallel work carried out in this laboratory provide evidence for the absence of a direct toxic action of endotoxin on the myocardium. Even though all support animals were severely damaged from the effects of endotoxin in the current series, as exhibited by extremely low arterial pressures and deaths occurring within 3 hr, isolated hearts performed normally as shown by cardiac work and power, dP/dT , LVEDP, and oxygen uptake.

Goodyer (11) pointed out that ventricular

TABLE IV. Effect of Endotoxin on PH, Oxygen Uptake, and Carbon Dioxide Production in the Isolated Heart Preparation Following β -Adrenergic Blockade (mean $\pm$ SE; $N = 6$).

Period		pH ^a	O ₂ uptake (ml/min/100 g left ventricle)	CO ₂ production (ml/min/100 g left ventricle)
Control	A	7.42 (±0.02)	9.7 (±1.3)	9.2 (±1.4)
	V	7.40 (±0.02)		
Post-β- adrenergic blockade (propranolol, 0.5 mg/kg)	A	7.41 (±0.03)	10.6 (±1.1)	10.3 (±1.2)
	V	7.38 (±0.03)		
Postendotoxin (LD ₅₀)				
20–30 min	A	7.30 (±0.02)	8.8 (±1.4)	10.9 (±1.2)
	V	7.28 (±0.02)		
50–75 min	A	7.21 (±0.05)	11.1 (±1.0)	7.1 (±0.9)
	V	7.20 (±0.05)		
80–125 min	A	7.20 (±0.08)	9.3 (±1.7)	6.8 (±1.8)
	V	7.20 (±0.08)		

^a A = coronary artery; V = coronary vein.

contractile capacity was enhanced in hemorrhagic and endotoxin shock as a result of increased sympathetic drive. Lefer and others, on the other hand, demonstrated the release of a cardiodepressant blood borne factor in hemorrhagic and endotoxin shock (7-10). It seemed conceivable to us that both the excitatory and depressant influences could be operative in endotoxin shock and tend to cancel each other's effects. However, results from the present study show that with the elimination of sympathetic influences on the heart by beta adrenergic blockade, which would be expected to unmask a depressor effect, there is no evidence of a circulating cardiodepressant factor in the blood of animals dying in irreversible shock. Cardiac performance appeared to be well maintained in part at least by increased coronary blood flow and decreased pH which should increase oxygen delivery to myocardial tissue (23). The increase in coronary blood flow could not have been due to catecholamine release since this action was clearly blocked by propranolol. Key factors in the mechanism of increased coronary flow in the present study are probably myocardial tissue oxygen tension and circulating vasodilator metabolites

(23). Thus, increased myocardial blood flow, achieved by marked coronary vasodilatation coupled with adequate extraction of oxygen from capillary blood, and the ability of the heart to achieve normal oxidative metabolism in a relative acid medium, provide the necessary essential ingredients for normal myocardial performance.

Results from the present study are in agreement with Weil and others (19), who found no electrocardiographic evidence for myocardial failure after endotoxin; Londe and others (24), who observed that endotoxin produced no perceptible effect on myocardial extraction of oxygen; Kutner and Cohen (25), who reported that lethal doses of endotoxin did not affect myocardial contractility; and Alican and others (26), who noted a resistance of the myocardium to endotoxin when arterial pressure is maintained.

Findings from the present study do not preclude the possibility of adverse effects of prolonged systemic hypotension and progressive peripheral pooling on cardiac performance, which most assuredly occur. The data clearly suggest, however, that myocardial performance is not damaged by direct or secondary toxic effects of endotoxin or

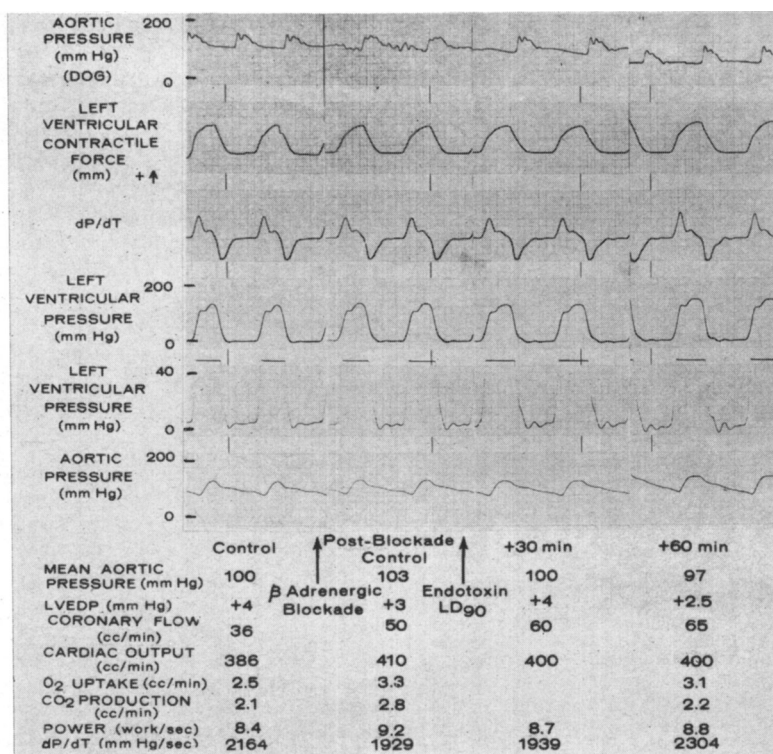


FIG. 3. Effects of endotoxin (LD_{50}) on cardiac hemodynamics, work performance, and metabolism during β -adrenergic blockade (representative experiment).

myocardial depressant substances, circulating in the blood of irreversibly shocked animals.

Summary. The question of the precise role of the heart in shock has been largely unresolved. Previous separate reports have shown that both excitatory and depressant actions on the myocardium after endotoxin are observed. The purpose of the present study was to assay the possibility of a direct myocardial toxic action of endotoxin or a circulating myocardial depressant factor released in the blood of endotoxin shocked animals. This was accomplished by utilization of beta adrenergic blockade (propranolol) under the experimental conditions of constant cardiac output and aortic pressure in an isolated canine heart preparation exchanging blood with an intact support animal shocked by endotoxin.

Results from the study fail to reveal a myocardial depressant effect following a lethal injection of endotoxin. Cardiac performance is relatively unimpaired after en-

dotoxin in the presence of beta adrenergic blockade as evidenced by normal cardiac work and power, dP/dT , LVEDP, and oxygen uptake. Myocardial performance is postulated to be maintained in the presence of endotoxin and shocked blood by increased coronary blood flow and effective oxyhemoglobin dissociation in an acid medium under conditions of maintained cardiac output and coronary perfusion pressure.

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