UNIVERSITY OF OKLAHOMA MEDICAL CENTER

EFFECTS OF ENDOTOXIN ON MYOCARDIAL HEMODYNAMICS, PERFORMANCE, AND METABOLISM

L. B. Hinshaw, L. T. Archer, L. J. Greenfield,
and C. A. Guenter

Technical Report No. 39
University of Oklahoma Medical Center THEMIS Contract

MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE
OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.
800 Northeast Thirteenth Street
Oklahoma City, Oklahoma 73104

Experiments investigating the cause of the decrease in cardiac output after endotoxin have demonstrated a decrease in venous return in both the canine and primate species (9,11-13,27). It appears therefore that systemic hypotension in endotoxin shock is in large part precipitated by peripheral rather than direct cardiac mechanisms.

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. It is postulated by some that heart failure is seen only late in shock subsequent to prolonged inadequate coronary perfusion (2). However, others have developed a "cardiac theory" which assumes that irreversible shock is due to a sustained depressed cardiac output of a dysfunctioning heart, failing as a relatively early event (14, 25). A cardiac-toxic theory has also been suggested in which a myocardial depressant factor is postulated to directly decrease cardiac performance (15-17).

The objective of the present study is to investigate the role of the heart in endotoxin shock, to determine if it is directly damaged by endotoxin or fails as a result of deleterious hemodynamic or respiratory alterations set into motion by the shock state.

Experiments designed to distinguish between direct and indirect cardiac factors, have been carried out and results exclude a direct cardiotoxic action of endotoxin; demonstrate a strong resistance of the myocardium in endotoxin shock; and suggest that myocardial failure may occur only after extensively prolonged systemic hypotension.

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 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 mm/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. To transfer the donor heart to the external perfusion system without interruption of coronary flow, the brachiocephalic outflow from the heart was opened, allowing blood to fill the tubing against a hydrostatic pressure in order to provide adequate coronary perfusion. 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 cc/minute, and the inferior vena cava was immediately ligated. Blood from the aortic outflow of the isolated heart was collected in a plastic reservoir (Figure 1) and returned to the dog, perfusing the heart 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 (3). 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 (Figure 1). Temperature of coronary venous blood was monitored with a temperature probe. Aortic pressure, left ventricular pressures, cardiac contractility of the isolated heart, and systemic pressure of the support dog 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. Coronary arterial and venous Po_2, Pco_2, and pH were followed by utilizing an Instrumentation Laboratories blood gas analyzer calibrated prior to each determination with known gas mixtures. 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 118 mm Hg with a cardiac output of 76 cc/min/kg body weight (based on the weight 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 thirty-minute control period in all experiments. At the end of the control period, an LD_{90} of E. coli endotoxin, 1.2 mg/kg (Difco, Detroit), was injected both intravenously into the support dog and into the pulmonary artery of the isolated heart. The mean coronary arterial pressure of the isolated heart was adjusted to that of the mean systemic pressure of the support animal by changing pulmonary blood flow rate with the blood pump. At 200 minutes post-endotoxin, coronary pressure and cardiac output were returned to pre-endotoxin values and cardiac performance, metabolic and hemodynamic parameters were evaluated. In addition, coronary pressure and cardiac output in all experimental and control studies were equalized at 60 and 180 minutes after zero time.

The control experiments, (N = 6) not given endotoxin, were conducted in order that mean coronary pressures and mean cardiac outputs of the isolated hearts were matched to those of the previous experimental group (N = 7) by pump adjustment at precisely the same times up to a terminal point of 200 minutes after zero time.

Stroke work in gram·meters was calculated from the formula used by others (19):

$$(MAP - LVEDP)\ (SV)\ (1.36)/100$$

where MAP = mean aortic pressure (mm Hg); LVEDP = left ventricular end diastolic pressure (mm Hg) and SV = stroke volume in cc, determined by dividing cardiac output by heart rate. The acceleration component of left ventricular stroke work was disregarded in the calculations on the basis that it represents less than 1 per cent of total stroke work (20). 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 (10,19) 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 (5).

Coronary blood flow averaged 160 cc/min/100 gms left ventricle at zero time (range 99-290) in 13 experiments.

Oxygen uptake was assumed to be negligible in atria and right ventricle (bypassed) as was reported by others (21) and averaged 11 cc/min/100 gms left ventricle at zero time (range 7-16 cc/min) in 13 experiments.

RESULTS

Figure 2 illustrates mean values for aortic pressure, cardiac output and blood temperature in control and endotoxin isolated working heart preparations. Mean aortic pressure changes in the endotoxin-series reflect alterations in mean systemic pressure of the support dog, except at the 200 and 180 minute readings when pressures were matched to zero time and 60 minute values respectively, by pump adjustment. Thus, two sets of matching points were achieved, one at the hypotensive value, and the last at the normotensive pressure level and cardiac output was similarly adjusted at the same time intervals. The mean values $\pm$ SE of the experimental group for blood temperature (T_b), cardiac output (CO) and aortic pressure (MAP) at 0 and 200 minutes respectively are as follows: T_b = 38.50 $\pm$ 0.54, 38.70 $\pm$ 0.37; CO = 482.7 $\pm$ 28.8, 481.6 $\pm$ 28.9; and MAP = 118.4 $\pm$ 4.2, 117.3 $\pm$ 3.9. These parameters were controlled because of their direct influence on performance, metabolic and hemodynamic characteristics of the myocardium (4, 21) and in order that the effects of endotoxin on the heart could be clearly discernable. In addition, control experiments were carried out after the completion of the endotoxin studies, with pressures and flows similarly matched by pump adjustment as in the experimental group. Results show no significant differences in values between the two series in all measured parameters at all recorded time periods.

With the foregoing protocol carefully executed, another set of parameters dealing with performance, metabolism and hemodynamics were measured or calculated and these are illustrated in the remaining figures.

Figure 3 characterizes the typical findings obtained in an isolated heart preparation treated with an LD_{90} of endotoxin. Only values during the matching periods, when pressures and flows were rigidly controlled, are shown in the figure. Results show that the heart performs normally both metabolically and

in regard to energy output at times of comparable aortic pressure and cardiac outputs after endotoxin administration. Findings at 180 minutes clearly resemble those at 60 minutes, while those at 200 minutes are very similar to those at -30 minutes and zero time. Thus, endotoxin is seen to have no adverse effects on myocardial performance characteristics including left ventricular contractile force, dP/dT_{max}, and power (work/sec) and no deleterious action was seen in the metabolic parameters of oxygen uptake and carbon dioxide production. Relationships between after-load (mean aortic pressure) and pre-load (left ventricular end diastolic pressure [LVEDP]) remained clearly similar during the control and post-endotoxin periods. Results strikingly demonstrate the notable effects of aortic pressure and cardiac output on contractility, dP/dT, coronary flow, LVEDP, power, and O_2 uptake and CO_2 production.

These results emphasize the importance of controlling pressure and flow in the isolated heart preparation in order to assay the effects of endotoxin. In order to compare the response of the heart exclusively to changes in aortic pressure and cardiac output in the absence of endotoxin, a second series of control experiments was carried out. Typical results from such an experiment are shown in Figure 4, and no significant differences in the response of any parameter from those of the endotoxin group are discernable from the various measurements and calculations of performance and metabolic characteristics.

Figure 5 summarizes mean results from control and endotoxin shock experiments. Particular evaluation of data was made at two time periods, 180 and 200 minutes, when aortic pressure and cardiac output are matched with earlier values at 60 minutes and zero time, respectively. The mean values $\pm$ SE of the experimental group for dP/dT_{max}, stroke work (SW), heart rate (HR),

power (P) and LVEDP at 0 and 200 minutes respectively are as follows: dP/dT_{max} = 2473 ± 173.00, 2658 ± 379.36; SW = 5.91 ± 0.37, 4.89 ± 0.34; HR = 127.1 ± 4.7, 146.4 ± 4.5; P = 12.41 ± 0.65, 11.90 ± 0.74; and LVEDP = 3.96 ± 1.20, 7.86 ± 4.03. It is seen that all parameters show similar changes regardless of the presence or absence of endotoxin. Findings clearly illustrate that the decreases of the various performance characteristics of the heart including dP/dT, stroke work and power, at 60 and 180 minutes ($p < 0.01$) are due to lowered aortic pressure and cardiac output, rather than endotoxin directly. When aortic pressure and flow are elevated to control values at 200 minutes (Figure 2), these performance characteristics return to the normal values observed at zero time. Mean LVEDP, though decreasing ($p \leq 0.05$) in the control at 60 minutes is insignificantly changed at 180 minutes. LVEDP is insignificantly decreased at 60 and 180 minutes in the endotoxin group and insignificantly elevated at 200 minutes when pressure and flow are restored in both the control and endotoxin series. The observed mean increase in LVEDP in both groups at 200 minutes was due to the fact that each group contained one experiment in which LVEDP was elevated above 20 mm Hg.

Figure 6 demonstrates the effects of endotoxin on coronary blood flow, coronary vascular resistance, oxygen uptake and carbon dioxide production. Coronary flow changes insignificantly ($p > 0.05$) in all experiments up to 180 minutes while coronary vascular resistance falls during the total post-endotoxin period in the experimental group ($p < 0.05$). Notable findings were the large increases in coronary flows occurring in both groups at 200 minutes greatly exceeding those during the control periods ($p < 0.05$). Both mean oxygen uptake and carbon dioxide production returned to control values at termination of all studies. The significant reduction of O_2

uptake and CO_2 production ($p \leq 0.05$) at 180 minutes is seen in both the control and endotoxin series. Mean RQ values from -30 to +200 minutes in endotoxin studies are 0.83, 0.90, 0.99, 0.88, 0.91 and in control experiment are 0.83, 0.76, 0.91, 0.86, 0.91. There were no significant changes in the RQ values.

Tables Ia and Ib summarize mean oxygen and carbon dioxide pressures, contents, and pH changes in coronary arterial and venous blood observed in both endotoxin and control experiments. It is noted that the endotoxin seri showed significant acidosis by 200 minutes ($p \leq 0.05$) while pH was seen to remain relatively constant in the control group. Coronary venous oxygen content was not elevated at termination of the endotoxin experiments although increases were seen in the control series. Results demonstrate a lower mean coronary venous oxygen content at the same mean Po_2 in the endotoxin treated heart in comparison to the control group at 200 minutes.

DISCUSSION

The primary purpose of the present study was to determine possible direct toxic effects of endotoxin on canine myocardial tissue. To this end, two kinds of experimental controls were devised and executed: (a) cardiac performance and metabolism were assayed after the end of a three hour period of hypotension by requiring the heart to work at the precise pre-shock levels of cardiac output and aortic pressure; and (b) the degree of hypotension and depressed cardiac output in the isolated heart preparation in shock studies was mimicked by pump adjustment in the absence of endotoxin. In addition, the heart was also evaluated at 180 minutes at cardiac output and aortic pressure values obtained at 60 minutes.

Three hours of systemic hypotension and depressed cardiac output followed by restoration of pressure and flow to control values by pump adjustment, revealed statistically insignificant differences in results between the endotoxin or control groups in which endotoxin was not administered. Myocardial contractility, cardiac power (work/sec.), dP/dT, O_2 uptake and CO_2 production at 200 minutes post-endotoxin were statistically unaltered from control pre-endotoxin values. These observations appear to preclude any significant direct toxic action of endotoxin on myocardial performance and metabolism. Although findings reveal a strong resistance of the myocardium to endotoxin, the effects of prolonged systemic hypotension may ultimately impair cardiac function. In single heart experiments in both the endotoxin and control series, LVEDP rose above control values at 200 minutes upon restoration of aortic pressure and cardiac output.

The studies show that the h-art treated with endotoxin exhibits marked changes in hemodynamics which appear to assure its high level of performance and metabolism: coronary flow markedly increases when the heart is required to work at the pre-shock level and the coronary venous oxygen content remains

at a normally low value, and oxygen uptake is adequately achieved even when pH has fallen to significantly depressed values. Thus, increased blood flow, achieved by marked coronary vasodilatation coupled with an adequate extraction of oxygen from capillary blood, and the ability of the heart to achieve normal oxidative metabolism in an acid medium provides the necessary essential requirements permitting the heart to operate at normal levels of performance. Results from the present study show that dP/dT, cardiac power and aortic pressure are directly related to oxygen uptake of the myocardium. These results are in agreement with the view that heart failure is probably only seen late in shock subsequent to prolonged inadequate coronary perfusion (2). No evidence was obtained to support recent observations in hemorrhagic and endotoxin shock, that a myocardial depressant factor is released which directly decreases cardiac performance (15-17). Results from the present study fail to reveal a single instance of endotoxin toxicity on myocardial work performance or oxidative metabolism. These observations support the conclusions of some investigators (2,5,18,27) but are in disagreement with others (14,23,24-26). The postulation that primary heart failure is an early event in shock (1,6-8), and initiates the irreversible state, is not supported by the findings of the present investigation.

The problem of the precise role of the heart in the development of irreversible endotoxin shock is complicated by events occurring in the periphery which most assuredly adversely influence cardiac output (9,11-13,22,27), causing its decrease on the basis of diminished venous return due to peripheral pooling of blood. In addition, the resultant prolonged systemic hypotension may assure the precipitation of a vicious cycle by virtue of the adverse effects of diminished coronary perfusion pressure and flow on myocardial integrity. Careful future consideration of adverse indirect hemodynamic or respiratory effects

on the myocardium is suggested from data in the present study in order to assay more clearly the role of the heart in septic shock (24,26).

*Acknowledgement: Appreciation is expressed to R. T. Brantley, Janet Camp, Hubert Jennings, Mary Lane, Susan Owen, Mary Marple, and Mary Carol Whitaker for valuable technical assistance.

REFERENCES

1. Albert, H. M., B. A. Glass, and R. L. Carter. The role of the heart in shock: Exsanguination studies. Ann. Surg. 34: 48-52, 1968.
2. Alican, F., M. L. Dalton, and J. D. Hardy. Experimental endotoxin shock: Circulatory changes with emphasis upon cardiac function. Am. J. Surg. 103: 702-708, 1962.
3. Boniface, K. J., O. J. Brodie, and R. P. Walton. Resistance strain gauge arches for direct measurement of heart contractile force in animals. Proc. Soc. Exptl. Biol. Med. 84: 263-266, 1953.
4. Braunwald, E., S. J. Sarnoff, R. B. Case, W. N. Stainsby, and G. H. Welch, Jr. Hemodynamic determinants of coronary flow: effect of changes in aortic pressure and cardiac output on the relationship between myocardial oxygen consumption and coronary flow. Am. J. Physiol. 192: 157-163, 1958.
5. Bugg-Asperheim, B., and J. Kjekshus. Left ventricular pressure and maximum rate of pressure rise as determinants of myocardial oxygen consumption during hemorrhagic hypotension in dogs. Acta Physiol. Scand. 78: 174-183, 1970.
6. Crowell, J. W., and A. C.Guyton. Evidence favoring a cardiac mechanism in hemorrhagic shock. Am. J. Physiol. 201: 893-896, 1961.
7. Crowell, J. W., and A. C. Guyton. Further evidence favoring a cardiac mechanism in irreversible hemorrhagic shock. Am. J. Physiol. 203: 248-252, 1962.
8. Crowell, J. Oxygen transport in the hypotensive state. Fed. Proc. 29: 1848-1853, 1970.
9. Gilbert, R. P. Mechanisms of the hemodynamic effects of endotoxin. Physiol. Rev. 40: 245-278, 1960.

10. Gleason, W. L., and E. Braunwald. Studies on the first derivative of the ventricular pressure pulse in man. J. Clin. Invest. 41: 80-91, 1962.

11. Hinshaw, L. B., R. P. Gilbert, H. Kuida, and M. B. Visscher. Peripheral resistance changes and blood pooling after endotoxin in eviscerated dogs. Am. J. Physiol. 195: 631-634, 1958.

12. Hinshaw, L. B., T. E. Emerson, Jr., and D. A. Reins. Cardiovascular responses of the primate in endotoxin shock. Am. J. Physiol. 210: 335-340, 1966.

13. Hinshaw, L. B., L. L. Shanbour, L. J. Greenfield, and J. J. Coalson. Mechanism of decreased venous return in subhuman primate administered endotoxin. Arch. Surg. 100: 600-606, 1970.

14. Kadowitz, P. J., and A. C. Yard. Circulatory effects of hydrocortisone and protection against endotoxin shock in cats. Europ. J. Pharm. 9: 311-318, 1970.

15. Lefer, A. M., P. Cowgill, F. F. Marshall, L. M. Hall, and E. D. Brand. Characterization of a myocardial depressant factor present in hemorrhagic shock. Am. J. Physiol. 213: 492-498, 1967.

16. Lefer, A. M., and M. J. Rovetto. Influence of a myocardial depressant factor on physiologic properties of cardiac muscle. Proc. Soc. Exptl. Biol. Med. 134: 269-273, 1970.

17. Lefer, A. M. Role of a myocardial depressant factor in the pathogenesis of circulatory shock. Fed. Proc. 29: 1836-1847, 1970.

18. Londe, S. P., H. Massie, W. W. Monafo, Jr., and H. R. Bernard. Resistance of the isolated canine heart to endotoxin. Surg. 61: 466-470, 1967.

19. Ross, J., Jr., E. H. Sonnenblock, G. A. Kaiser, P. L. Frommer, and E. Braunwald. Electroaugmentation of ventricular performance and oxygen consumption by repetitive application of paired electrical stimuli. Circ. Res. 16: 332-342, 1965.

20. Sarnoff, S. J., and E. Berglund. Ventricular function. I. Starling's Law of the Heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation. 9: 706-718, 1954.

21. Sarnoff, S. J., E. Braunwald, G. H. Welch, Jr., R. B. Case, W. N. Stainsby, and R. Macruz. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. Am. J. Physiol. 192: 148-156, 1958.

22. Selkurt, E. E. Status of investigative aspects of hemorrhagic shock. Fed. Proc. 29: 1832-1835, 1970.

23. Siegel, H. W., and S. E. Downing. Reduction of left ventricular contractility during acute hemorrhagic shock. Am. J. Physiol. 218: 772-779, 1970.

24. Siegel, J. H., M. Greenspan, and L. R. Del Guercio. Abnormal vascular tone, defective oxygen transport and myocardial failure in human septic shock. Ann. Surg. 165: 504-517, 1967.

25. Solis, R. T., and S. E. Downing. Effects of E. coli endotoxemia on ventricular performance. Am. J. Physiol. 211: 307-313, 1966.

26. Thal, A., and H. Bell. The peculiar hemodynamics of septic shock. Post Grad. Med. 48: 106-114, 1970.

27. Weil, M. H., L. D. MacLean, H. B. Visscher, and W. W. Spink. Studies on the circulatory changes in the dog produced by endotoxin from gram-negative microorganisms. J. Clin. Invest. 35: 1191-1198, 1956.

LEGEND FOR FIGURES

Figure 1. Schematic diagram of isolated perfused heart preparation . (Blood is obtained from aorta of support dog and subsequently returned to femoral vein. Arrows show direction of blood flow. Lungs are not ventilated.)

PA . . . . . .pulmonary artery

A. . . . . .aorta

BC . . . . . .brachiocephalic artery

RA . . . . . .right atrium

RV . . . . . .right ventricle

AZ . . . . . .azygous vein

SVC. . . . . .superior vena cava

IVC. . . . . .inferior vena cava

LVC. . . . . .left ventricular pressure catheter

CVC. . . . . .coronary drainage catheter

AC . . . . . .aortic pressure catheter

SC . . . . . .adjustable screw clamp

SGA. . . . . .strain gauge arch

TP . . . . . .temperature probe

WB . . . . . .water bath at controlled temperature

Figure 2. Parameters controlled in isolated heart experiments. Mean blood temperature is maintained relatively constant in both control and experimental preparations. Mean aortic pressures of endotoxin-treated hearts are matched with intact support animal following endotoxin injection (M ± S.E.), and values at 180 minutes and 200 minutes matched those at 60 minutes and zero time, respectively.

Cardiac output and mean aortic pressure of control isolated heart preparations are also matched with endotoxin shock studies by adjustment of pump and screw clamp (as shown in Figure 1).

Figure 3. Effects of endotoxin (LD_{90}) on performance and metabolism of isolated working heart. (Single experiment).

Figure 4. Single, control experiment showing effects of decreasing cardiac output and aortic pressure on myocardial performance and metabolis Mean aortic pressure and cardiac output values were adjusted to equal mean values of shock experiments at -30, 0, +60, +180, +200 minutes (adjustments were also made at 15 min. intervals).

Figure 5. Effects of endotoxin (LD_{90}) on myocardial performance characterist including dP/dT_{max}, stroke work, heart rate, power and left ventricular end diastolic pressure (mmHg). (M ± S.E.; 6 control and 7 endotoxin experiments). Mean aortic pressure and cardiac output values of all control heart preparations were adjusted to equal mean values of endotoxin studies at -30, 0, +60, +180, +200 minutes (Blood temperature constant).

Figure 6. Effects of endotoxin (LD_{90}) on myocardial hemodynamics and metabolism (M ± S.E.; 6 control and 7 endotoxin experiments). Mean aortic pressure and cardiac output values of all heart control and experimental preparations are equal at -30, 0, +200 minutes, and those at 60 and 180 minutes are also equal. (See Figure 2). (Blood temperature constant).

Table Ib. Coronary Arterial and Venous Blood Gas and pH Values (M ± S.E.)
(7 experimental and 6 control studies)

CONTROL SERIES

Parameter		Time (Minutes) -30	0	+60	+180	+200
pO_2	A	75(6)	66(7)	61(6)	55(4)	55(4)
	V	29(2)	28(2)	28(3)	27(2)	29(4)
O_2 Content	A	15.2(0.9)	14.3(0.9)	14.2(0.6)	13.7(0.9)	13.9(1.1
	V	7.5(0.9)	7.6(0.7)	7.2(0.6)	8.0(0.8)	8.8(0.6
pCO_2	A	31(2)	31(3)	31(3)	28(2)	23(3)
	V	34(3)	36(3)	34(4)	30(2)	26(3)
CO_2 Content	A	39.1(0.9)	40.1(1.3)	38.6(2.0)	34.6(1.2)	33.5(1.4
	V	45.8(1.6)	45.4(1.8)	45.0(2.5)	39.4(1.9)	37.8(1.9
pH	A	7.41(0.02)	7.42(0.04)	7.38(0.03)	7.42(0.02)	7.42(0.0
	V	7.39(0.03)	7.38(0.03)	7.37(0.04)	7.40(0.02)	7.42(0.0

Table Ia. Coronary Arterial and Venous Blood Gas and pH Values (M ± S.E.)
(7 experimental and 6 control studies)

ENDOTOXIN SERIES

Parameter		Time (Minutes) -30	0	+60	+180	+200
pO_2	A	73(4)	70(4)	60(4)	56(5)	61(6)
	V	23(1)	22(2)	23(2)	27(2)	30(5)
O_2 Content	A	14.0(1.0)	14.0(0.8)	11.9(2.3)	12.7(1.2)	12.0(1.7
	V	6.1(0.9)	5.8(1.0)	7.3(1.1)	6.8(1.2)	6.1(1.0
pCO_2	A	30(1)	30(2)	26(1)	26(5)	27(5)
	V	37(2)	34(2)	32(1)	31(4)	31(3)
CO_2 Content	A	39.2(0.9)	38.3(0.9)	28.5(1.0)	28.7(2.5)	27.0(2.9
	V	45.6(0.5)	45.8(0.8)	34.6(.12)	33.9(2.7)	32.3(3.0
pH	A	7.40(0.03)	7.42(0.03)	7.34(0.03)	7.30(0.06)	7.29(0.0
	V	7.38(0.03)	7.39(0.03)	7.31(0.03)	7.30(0.05)	7.28(0.0

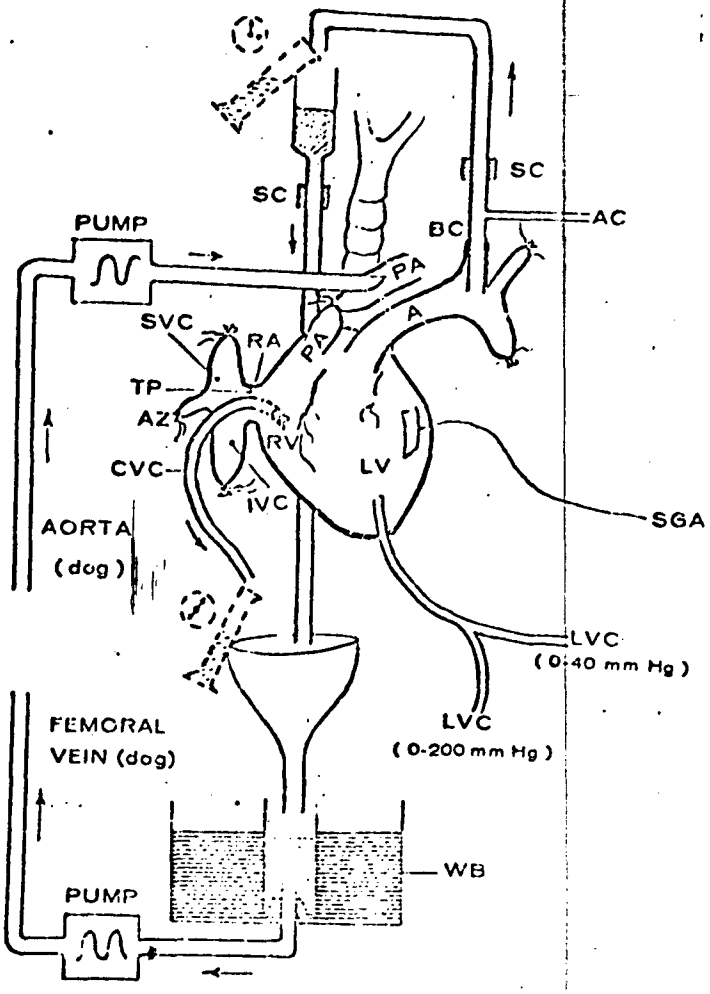

SC
SC
PUMP
BC
AC
PA
SVC
RA
PA
A
TP
AZ
RV
CVC
LV
IVC
SGA
AORTA
(dog)
LVC
(0-40 mm Hg)
FEMORAL
VEIN (dog)
LVC
(0-200 mm Hg)
WB
PUMP

FIGURE 1

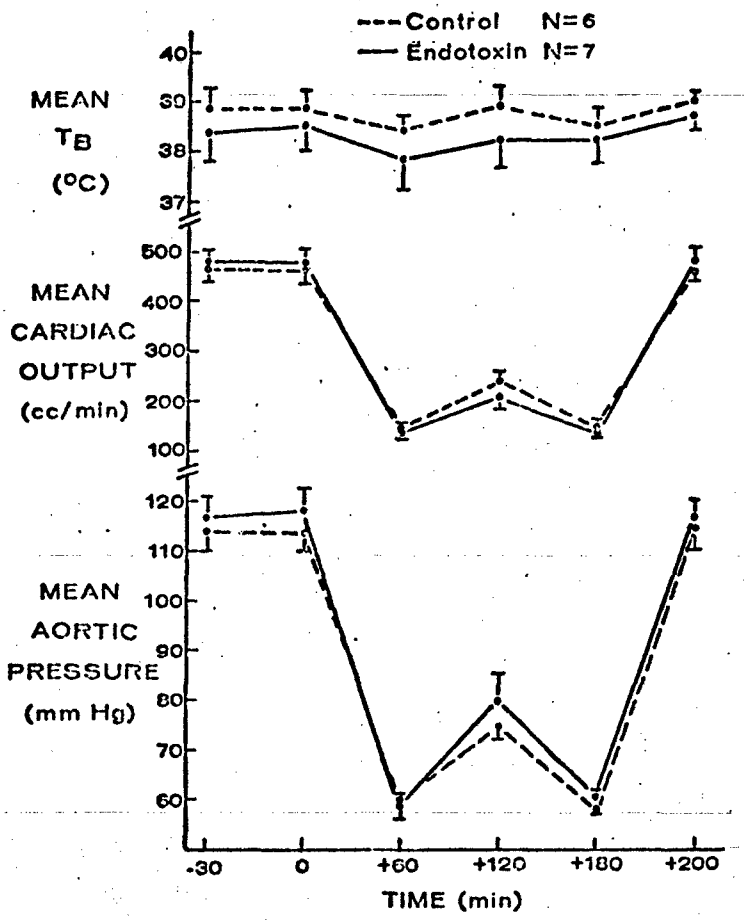
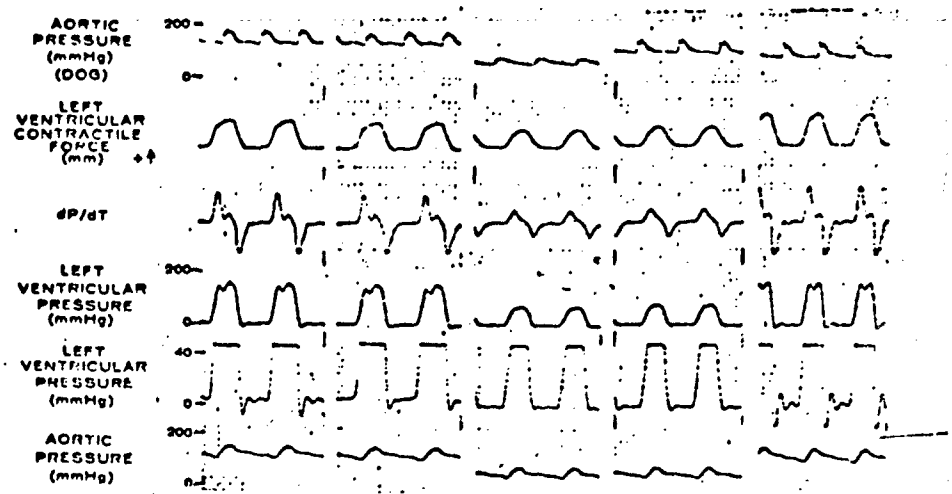
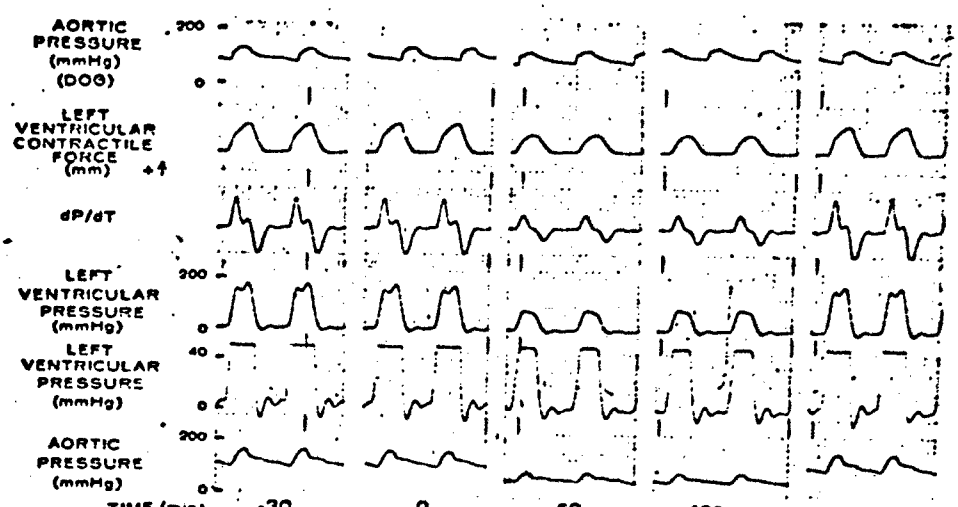

---Control N=6
—— Endotoxin N=7
MEAN
T_B
(°C)
40
39
38
37
MEAN
CARDIAC
OUTPUT
(cc/min)
500
400
300
200
100
MEAN
AORTIC
PRESSURE
(mm Hg)
120
110
100
90
80
70
60
-30
0
+60
+120
+180
+200
TIME (min)

FIGURE 2



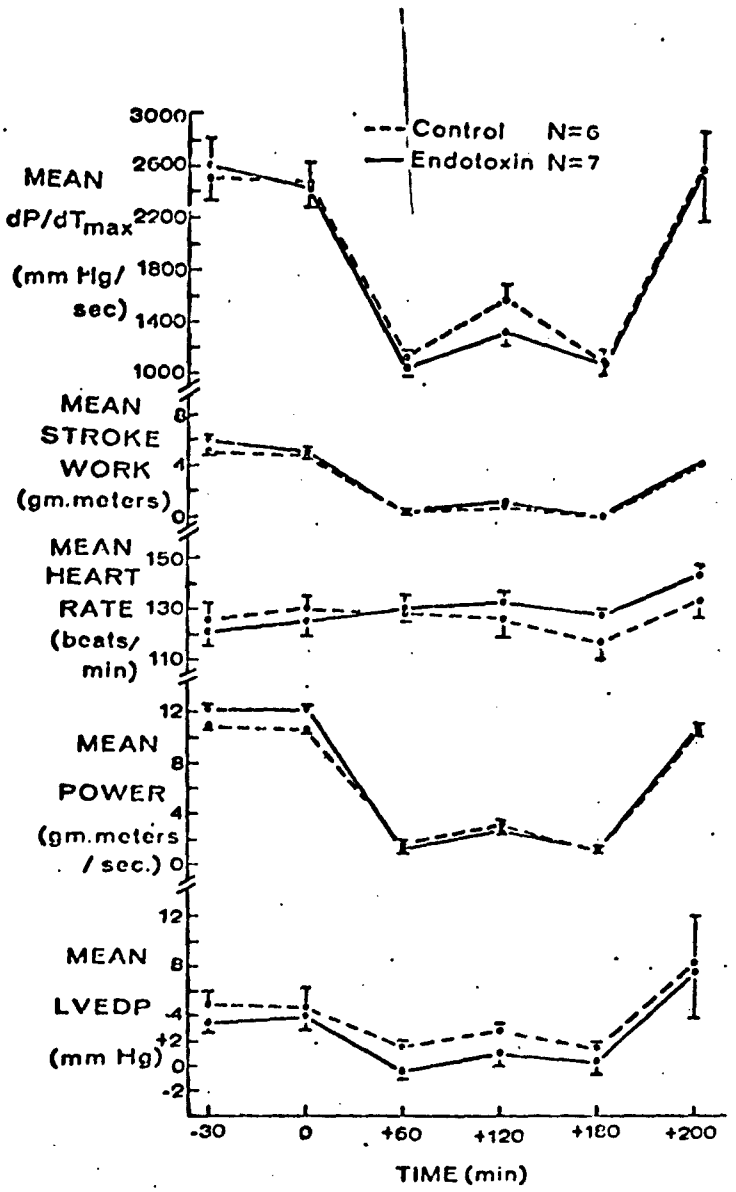
TIME (min)	-30	0	ENDO-TOXIN	+60	+180	+210
MEAN AORTIC PRESSURE (mmHg)	125	125		52	55	126
LVEDP (mmHg)	+3	+6		-1	0	+1.5
CORONARY FLOW (cc/min)	60	50		40	40	100
CARDIAC OUTPUT (cc/min)	510	510		165	165	515
O_2 UPTAKE (cc/min)	6.3	5.5		3.4	3.6	6.8
CO_2 PRODUCTION (cc/min)	4.6	5.3		2.6	3.0	6.1
POWER (work/sec)	14.1	13.8		2.0	2.1	14.5
dP/dT (mmHg/sec)	2575	2400		1050	1100	3200

FIGURE 3



TIME (min)	-30	0	60	180	200
MEAN AORTIC PRESSURE (mmHg)	118	118	56	56	118
LVEDP (mmHg)	+6	+5.5	+2	+1	+5.5
CORONARY FLOW (cc/min)	44	56	32	44	120
CARDIAC OUTPUT (cc/min).	504	496	162	164	510
O_2 UPTAKE (cc/min)	4.1	3.8	2.5	2.3	3.6
CO_2 PRODUCTION (cc/min)	3.3	2.5	1.5	2.6	3,7
POWER (work/sec)	12.8	12.7	2.0	2.0	13.0
dP/dT (mmHg/sec)	3400	3300	1250	1500	3700

FIGURE 4


Control N=6
Endotoxin N=7
MEAN dP/dT$_{max}$ (mm Hg/ sec)
3000
2600
2200
1800
1400
1000
MEAN STROKE WORK (gm.meters)
6
4
0
MEAN HEART RATE (beats/ min)
150
130
110
MEAN POWER (gm.meters / sec.)
12
8
4
0
MEAN LVEDP (mm Hg)
12
8
4
+2
0
-2
-30
0
+60
+120
+180
+200
TIME (min)

FIGUPE 5

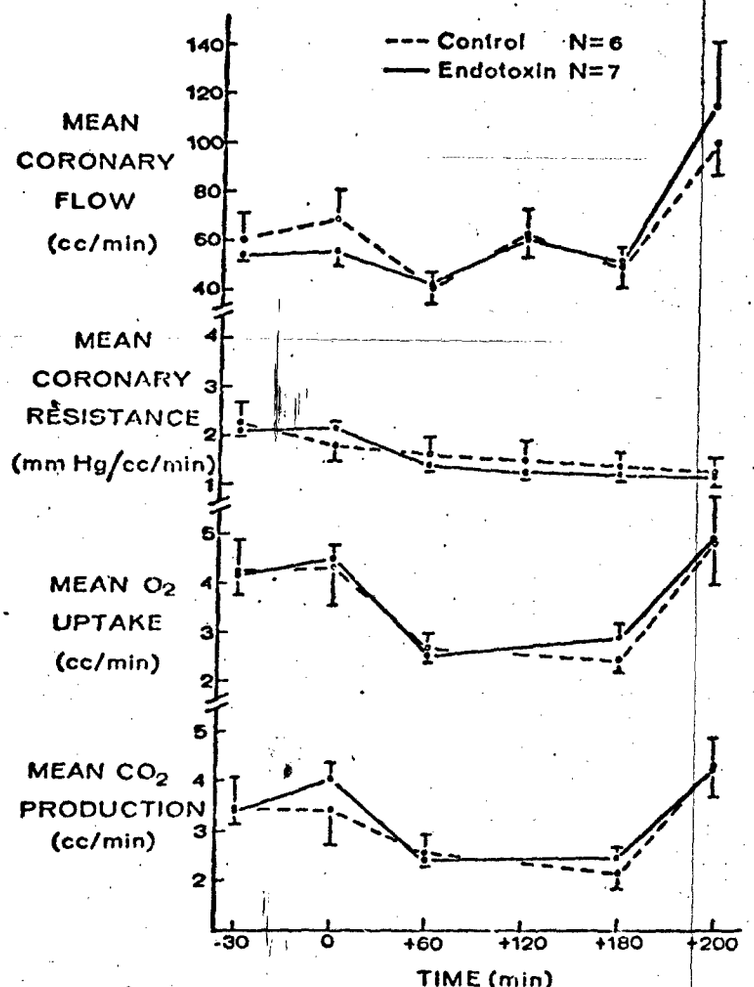

--- Control N=6
— Endotoxin N=7
MEAN CORONARY FLOW (cc/min)
140
120
100
80
60
40
MEAN CORONARY RESISTANCE (mm Hg/cc/min)
4
3
2
1
MEAN O_2 UPTAKE (cc/min)
5
4
3
2
MEAN CO_2 PRODUCTION (cc/min)
5
4
3
2
-30
0
+60
+120
+180
+200
TIME (min)

FIGURE 6

UNCLASSIFIED
Security Classification

DOCUMENT CONTROL DATA - R & D

Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)

MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.

2a. REPORT SECURITY CLASSIFICATION: UNCLASSIFIED

2b. GROUP: UNCLASSIFIED

3. REPORT TITLE

EFFECTS OF ENDOTOXIN ON MYOCARDIAL HEMODYNAMICS, PERFORMANCE, AND METABOLISM

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

Technical Report

5. AUTHOR(S) (First name, middle initial, last name)

L. B. Hinshaw, L. T. Archer, L. J. Greenfield, and C. A. Guenter

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
April 26, 1971	27	27

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
N00014-68-A-0496	
b. PROJECT NO. NR 105-516	39
c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	

10. DISTRIBUTION STATEMENT

This document has been approved for public release and sale; its distribution is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Office of Naval Research

13. ABSTRACT

The purpose of the present study was to determine possible direct adverse effects of endotoxin toxicity on canine myocardial tissue. Experiments were designed to assay cardiac performance, hemodynamics and metabolism in an isolated working left ventricle removed from a donor dog, exchanging blood with an intact support animal. Aortic pressure and cardiac output of the heart were decreased by pump adjustment in the experimental group to follow the support animal's mean systemic pressure after endotoxin or in the control group to mimic the previous cardiac endotoxin response. Three hours of systemic hypotension and depressed cardiac output followed by restoration of pressure and flow to control values by pump adjustment revealed insignificant differences between the endotoxin and control groups. Left ventricular end diastolic pressure, myocardial contractility, cardiac power (work/sec), dP/dT, O_2 uptake and CO_2 production were statistically unaltered from zero time control values after the sustained period of hypotension in both control and experimental groups. Findings indicate the absence of a direct toxic action of endotoxin on the myocardium.

26

DD FORM 1 NOV 65 1473 (PAGE 1)

S/N 0101-807-6811

UNCLASSIFIED
Security Classification