Br. J. Pharmac. (1975), **54**, 145-155

MYOCARDIAL FAILURE WITH ALTERED RESPONSE TO ADRENALINE IN ENDOTOXIN SHOCK

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1 There is a growing concensus that myocardial performance in the early stages of experimental endotoxic and septic shock is relatively normal; however, recent reports have identified an intermediate phase of shock when myocardial dysfunction is clearly apparent.

2 The mechanism of dysfunction has become a subject of intense investigation. A current view is that altered myocardial responsiveness to circulating catecholamines may play an important role in the dysfunction observed after endotoxin administration. The present studies, in which an isolated working heart preparation of the dog was used, were designed to test this hypothesis. This particular experimental preparation was selected to provide an adequate interpretation of results; cardiac output, afterload, and concentrations of adrenaline reaching the coronary vascular bed were controlled in all experiments. Responses to infusions of adrenaline were recorded in the 'steady-state' condition. Control (non-shocked) heart responses to adrenaline were highly reproducible in terms of inotropic, chronotropic and coronary vascular behaviour.

3 Results from the study document myocardial dysfunction within 4-6 h following an LD_{70} endotoxin administration on the basis of increased left ventricular end diastolic pressure (LVEDP), decreased cardiac power and myocardial efficiency, and depressed negative and positive dP/dt parameters.

4 Findings suggest significantly altered responsiveness of the myocardium to infused adrenaline at rates of 1, 2, and 5 μg/min with concentrations between 10 and 1 ng/ml blood. LVEDP was elevated while calculated power and efficiency parameters remained significantly below control values during infusion of adrenaline in endotoxin-treated hearts. Depressions of responsiveness were interpreted to occur on the basis of failure to restore positive and negative dP/dt to normal values and depressed coronary blood flow responses during adrenaline administration. Increases in coronary flow were regularly less in experimental hearts than the controls. Heart rate responses to adrenaline in both failing and non-failing hearts were identical.

5 In conclusion, it is suggested that myocardial contractile and relaxation characteristics and coronary vascular responses to adrenaline infusion are depressed in endotoxin shock during the period of demonstrated myocardial dysfunction. No distinct causal relationships were observed between the altered myocardial responsiveness and pathogenesis of heart dysfunction since myocardial dysfunction and altered responsiveness to adrenaline were generally observed together. Myocardial oedema formation after endotoxin as previously reported by this laboratory may bear a relationship to the depressed negative dP/dt response to adrenaline.

Introduction

Classically described early haemodynamic changes in endotoxin shock consist of progressive decreases in venous return and cardiac output occurring concomitantly with marked systemic hypotension in both canine (Weil, MacLean, Visscher & Spink, 1956; MacLean & Weil, 1956) and subhuman primate species (Hinshaw, Shanbour, Greenfield & Coalson, 1970). However, since early peripheral sequestration of blood is clearly observed to occur, the decrease in cardiac output has been accounted for on the basis of diminished venous return (Weil *et al.*, 1956). There is a growing concensus of opinion that myocardial performance in the early stages of shock (0-3 h) is relatively normal and

that depressed cardiac performance *per se* performs an insignificant role in the early reduction of cardiac output (Weil *et al.*, 1956; Goodyer, 1967; Hinshaw, Archer, Greenfield & Guenter, 1971a; Hinshaw, Archer, Greenfield, Guenter & Miller, 1972a; Hinshaw, Greenfield, Owen, Black & Guenter, 1972c; Siegel, Farrell, Goldwyn & Friedman, 1972). It has been proposed by Goodyer (1967) and Hinshaw *et al.* (1971a) and inferred from the work of Siegel *et al.* (1972) that ventricular performance in the initial stage of endotoxin or septic shock is supported by a sympathoadrenal response initiated subsequent to the development of systemic hypotension, which is consistent with the findings of others (Nykiel & Glaviano, 1961; Hökfelt, Bygdeman & Sekkenes, 1962; Cavanagh, Rao, Sutton, Bhagat & Bachmann, 1970; Hall & Hodge, 1971). Increased neurohumoral activity associated with the early compensatory period of shock should provide substantial cardiovascular support toward the maintenance of normal haemodynamics in the face of diminished venous return.

Recent reports have identified a subsequent phase of shock, following the early compensatory period, when myocardial performance begins to falter or fail altogether (Solis & Downing, 1966; Goodyer, 1967; Siegel, Greenspan & Del Guercio, 1967; Cavanagh *et al.*, 1970; Bell & Thal, 1970; Cann, Stevenson, Fiallos & Thal, 1972; Hinshaw *et al.*, 1972c; Hinshaw, Archer, Black, Greenfield & Guenter, 1973; Parratt, 1973; Nishijima, Weil, Shubin & Cavanilles, 1973; Hinshaw, Archer, Black, Elkins, Brown & Greenfield, 1974a; Parratt & Winslow, 1974; Greenfield, Jackson, Elkins, Coalson & Hinshaw, 1974) in both animal endotoxic studies and clinical septic shock. The observed myocardial dysfunction in not merely a preterminal event and is not necessarily associated with systemic hypotension, acidemia, or depressed oxygen delivery (Hinshaw *et al.*, 1972c, 1973; Hinshaw, Archer, Spitzer, Black, Peyton & Greenfield, 1974b), and does not appear to be due to the release of a myocardial depressant factor (Hinshaw, Greenfield, Owen, Archer & Guenter, 1972b; Hinshaw *et al.*, 1974a). One possible cause of the dysfunction may be a depressed response of the myocardium to circulating catecholamines following the period of increased sympathetic activity, and this potential mechanism is the subject of the present study. Recent research, supportive of this view, is that of Cavanagh *et al.* (1970), Bhagat, Cavanagh, Merrild, Rana & Rao (1970), and Parratt (1973), who reported depressed inotropic, chronotropic or altered coronary blood flow responses in various species of animals subjected to endotoxin shock. Relatively depressed myocardial responsiveness to neurally-induced sympathetic stimulation in shock has been reported by Glaviano & Klouda (1965) and Geocaris, Quebbeman, Dewoskin & Moss (1973). On the other hand, excessive sympathetic stimulation of the myocardium in rabbits administered endotoxin may elicit subendocardial haemorrhage and necrosis of myocardial fibres (Palmerio, Ming, Frank & Fine, 1962). Results from the present study partially support the earlier observations by Cavanagh *et al.* (1970), Bhagat *et al.* (1970), and Parratt (1973) once myocardial failure is clearly demonstrated, but provide no evidence for their initiating roles in the pathogenesis of myocardial dysfunction.

Methods

Experiments were carried out on nineteen isolated working canine hearts supported with arterial blood from a heparinized support dog, prepared as previously described (Hinshaw *et al.*, 1971a, 1973). The donor dog was anaesthetized, and the chest opened by median sternotomy after the animal was placed on a constant volume respirator. The azygos 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 venae cavae. The pericardial sac was opened along its ventral surface and the animal was injected with heparin (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 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 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 started at about 120 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 placed within a heated water bath, and returned to the dog at a flow rate equal to the superior vena caval inflow. Heart, lungs and adjoining tissue were then removed from the chest and supported by the trachea in the external system with adequately provided coronary pressure and blood flow. The lungs of the isolated heart were ventilated, while the support animal was respired spontaneously. Hearts were removed without interruption of blood flow from adult donor animals weighing between 4.5 and 8.0 kg and continuously supported by pump-delivered

blood from adult support dogs weighing between 22 and 32 kg.

The right heart was then bypassed after first passing 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 retrogradely perfused with blood by hydrostatic pressure from the aortic outflow tubing. Left ventricular pressure was measured simultaneously for end diastolic pressure (0-40 mmHg) and systolic pressure (0-200 mmHg) 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.

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 stopwatch. 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 continuously recorded by means of a resistance-capacitance differentiating network. Mean aortic pressure was controlled in the isolated heart preparation by adjustment of a screw clamp on the aortic outflow. Cardiac output was maintained at 76 ml kg^{-1} min^{-1} by adjustment of pump speed supplying the pulmonary artery.

Following an equilibrium period of approximately 30 min when a steady-state condition was reached, samples of coronary arterial and venous blood were collected and analyzed for blood gases, with an Instrumentation Laboratories blood gas analyzer. Oxygen content in coronary arterial and venous blood was measured by a Van Slyke manometric blood gas analyzer. Blood temperatures of isolated heart and support dog were measured continuously with thermistor probes and held constant by use of heating pads and water bath temperature regulation. Methods used for experimental procedures and statistical treatment of data have been described previously (Hinshaw *et al.*, 1974a, 1974b).

All isolated hearts received periodic and variable dose infusions of adrenaline (Parke, Davis & Co.) introduced into the left ventricle via a polyethylene catheter whose distal tip was placed in the chamber of the left atrium with the proximal end attached to a motor-driven syringe. Following measurement of control myocardial parameters without adrenaline, dose-response curves were carried out at regular intervals, all values being recorded during steady-state conditions. Adrenaline infusion rates were varied between 1, 2 and 5 μg/minute. These rates of infusion resulted in adrenaline blood concentrations of 1-10 ng/ml, based on the dilution of the infused drug with the cardiac output (average, 500 ml/min). Adrenaline was infused at afterloads of 50 mmHg and a cardiac output of 76 ml min^{-1} kg^{-1}, based on the weight of the heart donor animal. Afterloads were maintained at 100 mmHg between adrenaline infusions.

A control group of six hearts, receiving no endotoxin, was monitored at 100 and 50 mmHg afterloads for 4-5 h after the beginning of the heart perfusion period when pressures and flows became stabilized. Inotropic, chronotropic and coronary vascular responses to adrenaline infusions administered to control (non-shocked) hearts demonstrated a high degree of reproducibility during the 4-5 h period in the isolated state.

The experimental group consisted of thirteen isolated hearts and support animals receiving an LD_{70} dose of *Escherichia coli* endotoxin, 1.5 mg/kg. Endotoxin was obtained from Difco Laboratories, Detroit, Michigan (Lipopolysaccharide B, *E. coli* 0127 : B8, Boivin procedure with TCA extraction). The degree of lethality was previously determined on a group of 30-40 animals.

Seven anaesthetized support dogs and seven heart donor animals administered endotoxin were observed approximately 1-2 h before isolation of the left ventricle and its removal to the perfusion apparatus. In addition, six hearts and their respective support dogs were given endotoxin following transfer, equilibration and sampling for control values. As in the control group, samples were taken at 100 and at 50 mmHg afterload, and adrenaline responses were reported at 50 mmHg. Experimental and control isolated heart preparations were observed alike during the 4-5 h period in the isolated state.

Results

Results are divided into three categories: (a) those describing the effects of endotoxin on the support animal supplying blood to the isolated heart; (b) those documenting the development of myocardial dysfunction in the isolated heart during the 6 h post-endotoxin period; and (c) those illustrating changes in myocardial function (LVEDP, + and $-dP/dt_{max}$), work performance (power), heart rate, and myocardial

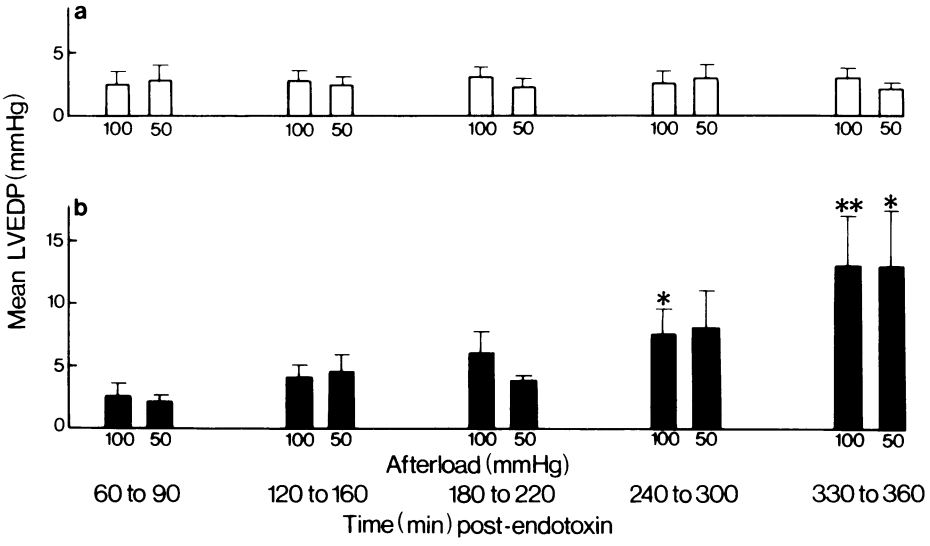

Figure 1 Changes in left ventricular end diastolic pressure (LVEDP) following administration of endotoxin (mean ± s.e., afterloads of 100 and 50 mmHg). Isolated canine hearts, (a) 6 control (no endotoxin), and (b) 13 experimental preparations, 0-6 h post-endotoxin. * $P < 0.05$; ** $P < 0.01$.

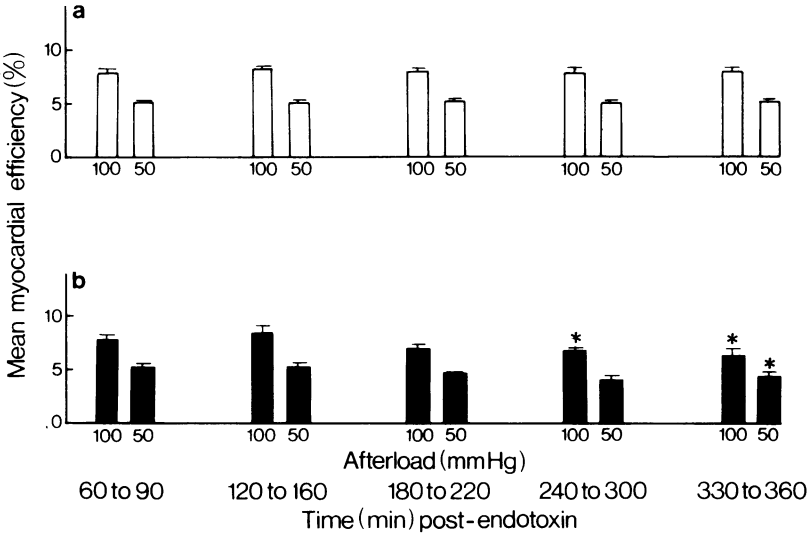

Figure 2 Effects of endotoxin on myocardial efficiency (mean ± s.e., afterloads of 100 and 50 mmHg). (a) 6 control (no endotoxin) and (b) 13 experimental heart preparations studied 0-6 h post-endotoxin. * $P < 0.05$; ** $P < 0.01$.

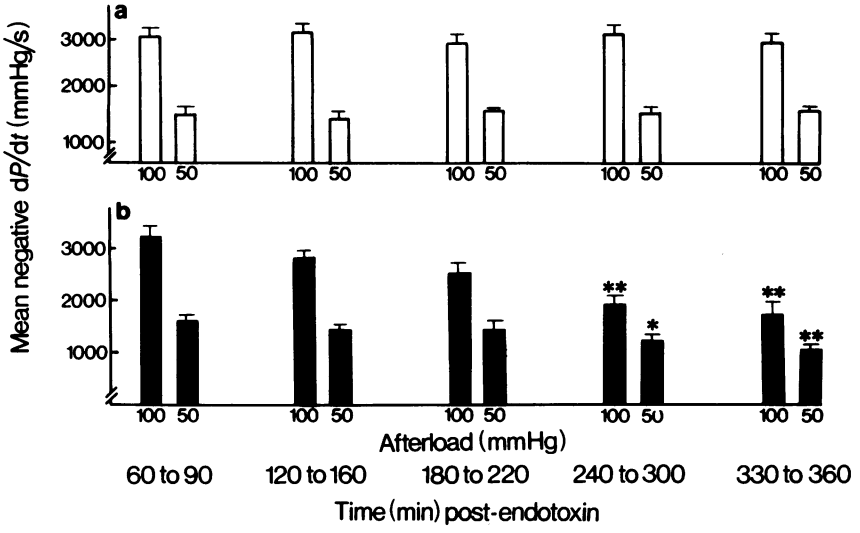

Figure 3 Decreases in mean negative dP/dt ($-dP/dt$) in (a) 6 isolated control (no endotoxin) hearts and (b) 13 experimental hearts studied 0-6 h post-endotoxin (mean ± s.e.). $*P < 0.05$; $**P < 0.01$.

haemodynamics (coronary blood flow) in response to graded doses of infused adrenaline.

Table 1 describes responses of support animals used in the current series of experiments to endotoxin administration and documents the sustained presence of systemic hypotension, in contrast to the normally maintained systemic pressures in control dogs not receiving endotoxin.

Figures 1, 2 and 3 and Table 2 illustrate the development of detrimental myocardial performance characteristics documenting cardiac dysfunction after endotoxin in the current series of heart studies. No statistically significant differences between experimental and control hearts were seen in the observed parameters until 4 h after endotoxin injection. Data from thirteen experimental heart preparations demonstrate significant elevations in left ventricular end diastolic pressure (LVEDP) ($P < 0.05$, Figure 1), depressions in myocardial efficiency ($P < 0.05$, Figure 2), negative dP/dt_{max} ($P < 0.05$, Figure 3), and positive dP/dt_{max} ($P < 0.05$, Table 2) at afterloads of 100 and 50 mmHg between 4 and 6 h post-endotoxin. The most outstanding readily

Table 1 Systemic arterial pressure response* of heart-support animals following LD_{70} endotoxin administration

Time post-endotoxin (min)	*Experimental group (n = 13)*	P	*Control group (n = 6)*
+60 to	85(7)	< 0.01	143(5)
+90	85(5)	< 0.01	133(5)
+120 to	80(8)	< 0.01	138(8)
+160	81(6)	< 0.01	138(8)
+180 to	104(9)	< 0.01	138(6)
+220	109(7)	< 0.05	137(7)
+240 to	90(8)	< 0.01	143(5)
+300	91(6)	< 0.01	133(5)
+330 to	83(10)	< 0.01	138(6)
+360	90(6)	< 0.01	137(7)

* mmHg; mean with (s.e. mean)

observable changes signalling the onset of myocardial dysfunction are increases in LVEDP to values exceeding 10 mmHg at low afterloads and progressively developing depressions of negative dP/dt. The possible significance of the latter is discussed in a recent report (Hinshaw *et al.*, 1974b).

Table 3 summarizes steady-state changes in myocardial O_2 uptake following endotoxin administration. In general, mean O_2 uptake values are lower in the experimental hearts compared with the controls not receiving endotoxin, and are significantly decreased within 4-5 h at afterloads of 50 and 100 mmHg, and from 5-6 h post-endotoxin at 50 mmHg ($P < 0.05$). Myocardial arterial P_{O_2} was significantly decreased ($P < 0.05$) from 2-5 h after endotoxin, maximum decreases ranging from an initial value of 112(±6) to 98(±3) mmHg at 5 hours.

Figures 4-6 summarize steady-state responses of the isolated heart preparation to different concentrations of adrenaline at various times following endotoxin during controlled afterloads and cardiac outputs. Control hearts not receiving endotoxin are similarly infused with adrenaline at the same time intervals. Adrenaline is infused into the left atrium during a fixed cardiac output (76 ml min^{-1} kg^{-1}, in order to avoid problems of variable dilution of adrenaline in the pulmonary bed and to insure delivery of identical adrenaline concentrations to the coronary bed. Afterloads were fixed at 50 mmHg in order to insure identical coronary perfusion pressure characteristics. All responses shown are steady-state values, ordinarily

Table 2 Changes in left ventricular positive dP/dt* ($+dP/dt$) following endotoxin administration

Time post-endotoxin (min)	*Afterload (mmHg)*	*Experimental group (n = 13)*	P	*Control group (n = 6)*
+60 to	100	2281(125)		2120(115)
+90	50	1295(45)		1200(75)
+120 to	100	2030(135)		2055(85)
+160	50	1145(65)		1110(40)
+180 to	100	2040(150)		2110(90)
+220	50	1160(50)		1185(65)
+240 to	100	1715(135)	< 0.05	2120(115)
+300	50	1075(45)		1200(75)
+330 to	100	1675(80)	< 0.01	2110(90)
+360	50	945(90)	< 0.05	1185(65)

* mmHg/s; mean (± s.e.) (76 ml min^{-1} kg^{-1} cardiac output at all afterloads)

Table 3 Changes in O_2 uptake* following endotoxin administration

Time post-endotoxin (min)	*Afterload (mmHg)*	*Experimental group (n = 13)*	P	*Control group (n = 6)*
+60 to	100	11.3(1.0)		12.0(0.6)
+90	50	8.5(0.7)		9.0(0.5)
+120 to	100	9.8(1.6)		11.3(0.4)
+160	50	7.6(1.2)		9.0(0.4)
+180 to	100	11.9(0.8)		11.9(0.5)
+220	50	9.1(0.7)		8.9(0.6)
+240 to	100	10.1(0.6)	< 0.05	12.0(0.6)
+300	50	7.6(0.4)	< 0.05	9.0(0.5)
+330 to	100	10.7(0.5)		11.9(0.5)
+360	50	7.0(0.7)	< 0.05	8.9(0.6)

* ml min^{-1} per 100 g left ventricle; mean (± s.e.)

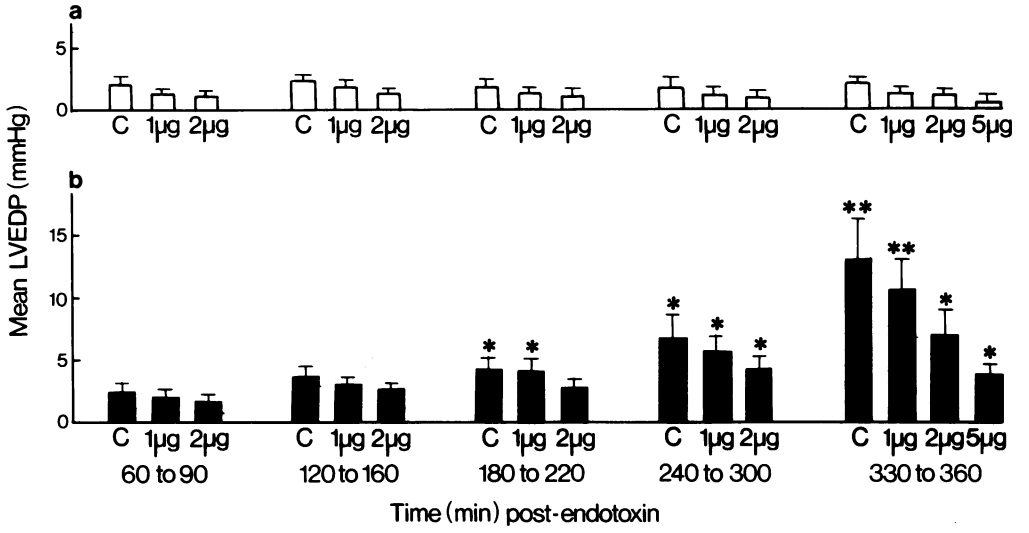

Figure 4 Mean steady-state values (± s.e.) of left ventricular end diastolic pressure (LVEDP) during adrenaline infusion into left atrium of isolated heart after endotoxin (LD_{70}). (a) Six control (no endotoxin) and (b) 13 experimental hearts studied 0-6 h post-endotoxin. * $P < 0.05$; ** $P < 0.01$.

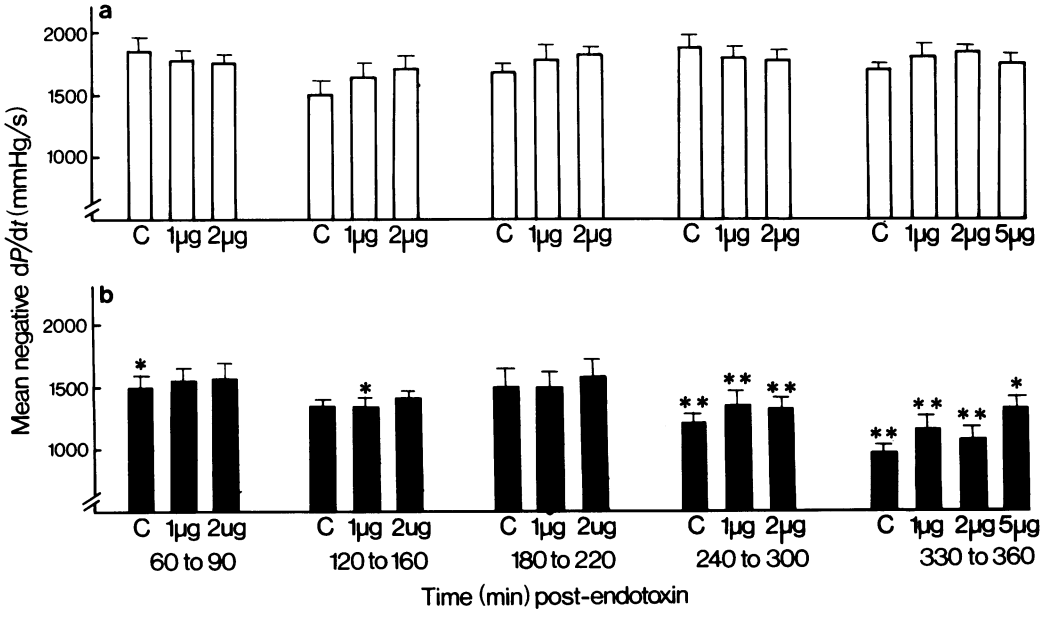

Figure 5 Mean steady-state values (± s.e.) of left ventricular negative dP/dt ($-dP/dt$) during adrenaline infusion into left atrium, 0-6 h post-endotoxin. (a) Six control (no endotoxin) and (b) 13 experimental hearts. * $P < 0.05$; ** $P < 0.01$.

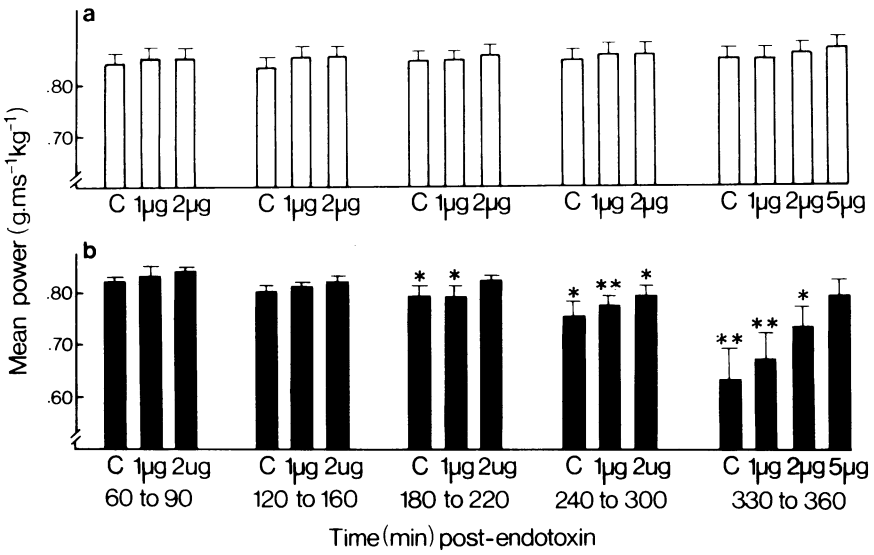

Figure 6 Mean steady-state values of left ventricular power ($g.m\,s^{-1}\ kg^{-1}$) during left atrial infusions of adrenaline 0-6 h after endotoxin. (a) Six control (no endotoxin) and (b) 13 experimental hearts (mean ± s.e.). * $P < 0.05$; ** $P < 0.01$.

achieved within 2-4 min of adrenaline infusion. The upper panel of Figure 4 shows mean LVEDP responses of six control hearts (no endotoxin) to adrenaline during a 4-5 h period. Results show that successive responses to 1 and 2 μg/min infusions of adrenaline in control hearts are reproducible and indistinguishable in magnitude at the same doses. On the other hand, the lower frame of Figure 4 shows that values of LVEDP in endotoxin-treated hearts are considerably higher, and significant differences occur between control and experimental (endotoxin) preparations from 3-6 h after endotoxin before and during adrenaline administration ($P < 0.05$). LVEDP values in failing hearts decreased during infusion of adrenaline but remained consistently higher than those from hearts not subjected to endotoxin at 1, 2 and 5 μg/min infusions ($P < 0.05$). Probability values shown in Figure 4 refer to differences between control (no endotoxin) and experimental (endotoxin) groups in response to adrenaline infusion at the same time interval.

Figure 5 shows negative dP/dt_{max} values in response to adrenaline infusion, as administered in the previous figure. Results from dysfunctioning hearts show decreases in negative dP/dt_{max} ($P < 0.05$) during the later phase of shock (4-6 h), which were little changed by the administration of adrenaline. Decreases in positive dP/dt_{max} were evident at 6 h post-endotoxin during adrenaline infusions of 1 and 2 μg/min ($P < 0.05$). Depressions in myocardial power are observable within 3 h after endotoxin and decline progressively ($P < 0.05$) up to the sixth hour (Figure 6). Infusions of 1 and 2 μg/min adrenaline failed to restore myocardial power to normal values ($P < 0.05$). At termination of the experiments, 5 μg/min adrenaline was infused and restored power to control values.

Coronary blood flow after endotoxin was higher during the early phase of shock than in the control non-shocked heart, reaching a peak of 96 ml min^{-1} per 100 g left ventricle (control, 78 ml/min) at 2 h post-endotoxin, thereafter declining steadily to 72 ml/min (control, 73 ml/min) within 6 hours. Mean increases in coronary blood flow in response to 1-2 μg/min infusions of adrenaline were regularly less in experimental hearts than the controls ($P < 0.05$), and this is particularly evident by 6 h of shock during an infusion of 5 μg/min adrenaline ($P < 0.05$). Results indicate that heart rate changes after endotoxin were no different from control non-shocked preparations. Heart rate responses to adrenaline infusions of 1, 2 and 5 μg/min were identical in both control and experimental hearts, showing notable increases in both series. At termination of the studies, during 5 μg/min infusions, rates of experimental hearts increased from 144 to 170 while controls were elevated similarly from 143 to 168 beats/minute.

Discussion

The primary initial factors previously reported to be instrumental in lowering cardiac output during the first 1-2 h of endotoxin shock are peripheral vascular pooling, extravasation of plasma, and the resultant effect of decreased venous return (Weil *et al.*, 1956; MacLean & Weil, 1956; Hinshaw, Shanbour, Greenfield & Coalson, 1970). Myocardial performance in the early phase of shock appears to be relatively normal (Goodyer, 1967; Hinshaw *et al.*, 1971a, 1972a; Hinshaw, Greenfield, Archer & Guenter, 1971b), and the subsequent induction of systemic hypotension elicits sympathoadrenal stimulation of the heart, augmenting its function (Nykiel & Glaviano, 1961; Hökfelt *et al.*, 1962; Cavanagh *et al.*, 1970; Hall & Hodge, 1971; Hinshaw *et al.*, 1971a; Siegel *et al.*, 1972; Geocaris *et al.*, 1973).

Substantial evidence has been produced for a prominent role of the myocardium in the ultimate development of irreversible endotoxin (septic) shock in a wide spectrum of animal species and in man himself (Hinshaw, 1974). The purpose of the present study was to evaluate adrenergically related mechanisms which might account for the eventual depression of myocardial function occurring from 2-6 h after administration of endotoxin or live *E. coli* organisms, as reported by Goodyer (1967), Cavanagh *et al.* (1970), Hinshaw *et al.* (1972c, 1973), Parratt (1973), Parratt & Winslow (1974), and Greenfield, Jackson, Elkins, Coalson & Hinshaw (1974). It was hoped that similar mechanisms to those observed in certain mammalian species might also apply to an understanding of the development of heart dysfunction in clinical septic shock (Siegel *et al.*, 1967, 1972; Bell & Thal, 1970; Cann *et al.*, 1972; Nishijima *et al.*, 1973).

One possible cause of cardiac dysfunction as studied in the present investigation was an altered myocardial responsiveness to circulating catecholamines which could presumably reduce cardiac output. Substantial evidence for this possibility has been presented by others (Cavanagh *et al.*, 1970; Bhagat *et al.*, 1970; Parratt, 1973). Limitations of these earlier reports were that either only portions of the heart were used in the tests for responsiveness, excluding the left ventricle itself, or that provisions were lacking to insure a constant delivery of catecholamine to the myocardial coronary circulation after the induction of shock. The methodology of the present study, while fixing cardiac inflow (cardiac output) and afterload at constant values (76 ml min^{-1} kg^{-1} and 50 mmHg, respectively) in the isolated working heart preparation during constant infusion rates of adrenaline into the left ventricle, rather than peripheral vein, assured better controlling features of the experiments for adequate interpretation of the data. Another advantage of the present preparation was that responses of control (non-shocked) hearts to adrenaline were found to be highly reproducible during a 4-5 h period of observation. Responses of experimental hearts, on the other hand, were notably different.

Results from the present study document myocardial dysfunction within 4-6 h after an LD_{70} endotoxin administration, as evidenced by statistically significant elevations of LVEDP and depressions of myocardial efficiency, power, and negative and positive dP/dt_{max} at afterloads of 50 and 100 mmHg. Intact support dogs, exchanging blood with the isolated heart and also receiving endotoxin, were markedly hypotensive during the 6 h observation period. The notable decrease in negative dP/dt_{max} values is considered to be associated with diminished effectiveness of cardiac filling during diastole (Hinshaw *et al.*, 1974b).

Findings from the present study suggest significantly altered responsiveness of certain myocardial performance and haemodynamic parameters to adrenaline infusions in hearts receiving endotoxin. LVEDP values in failing hearts decreased during administration of adrenaline but remained consistently higher than those in control hearts, even when high concentrations of adrenaline (5 μg/min) were used to challenge the myocardium. Decreases in both positive and negative dP/dt_{max} in dysfunctioning hearts could not be restored to normal by adrenaline infusion, and this was particularly noted by the observed negative dP/dt_{max} responses, presumably reflecting impaired cardiac filling characteristics. On the other hand, large doses of adrenaline (5 μg/min) essentially restored cardiac power calculations to normal in failing hearts, which was apparently due to improved cardiac contractility characteristics. Mean increases in coronary blood flow in response to adrenaline infusion were regularly less in experimental hearts than the controls, and this observation may bear a causal relationship to the development of heart dysfunction after endotoxin. This was particularly evident within 5-6 h of shock during an infusion of 5 μg/min adrenaline ($P < 0.05$). Heart rate, in contrast, responded similarly to adrenaline in both failing and non-failing (control) preparations. These findings suggest relatively depressed responsiveness of the canine heart model to adrenaline administration during the development of myocardial failure. Depressed myocardial efficiency and decreased inotropic and coronary blood flow responses to adrenaline were regularly

observed while chronotropic characteristics were not modified in the shocked state. These results are in agreement with Parratt's study (1973) in endotoxin-treated cats, except that a decreased chronotropic responsiveness to adrenaline was also reported. Bhagat *et al.* (1970) observed a reduced sensitivity of isolated guinea-pig atria to noradrenaline after endotoxin which reached a maximum depression within 6-18 h after endotoxin administration. Cavanagh *et al.* (1970) described a depressed responsiveness of the isolated baboon atrium to noradrenaline within 4 h after endotoxin. These guinea-pig and baboon atrial responses bear distinct similarities to our canine heart results with adrenaline, both as to type of depression and time required for its appearance after endotoxin.

Reasons for reduced responsiveness to adrenaline or noradrenaline are not known. In an interesting recent investigation, Drucker, Pindyck, Brown, Elwyn & Shoemaker (1974) pointed out that hypertonic glucose infusion in patients greatly enhanced the myocardial inotropic effect of administered glucagon. The augmented myocardial response to glucagon in the presence of adequate glucose included increased cardiac output and left ventricular stroke work. In a recent study (Hinshaw, Peyton, Archer, Black, Coalson & Greenfield, 1974c), a significantly increased survival rate was observed when hypoglycemia elicited by endotoxin in dogs was prevented by infusing hypertonic glucose in amounts sufficient to maintain arterial blood glucose concentrations constant. In view of both this study and the findings of Drucker *et al.* (1974), it might be surmised that myocardial inotropic responses to catecholamines in shock could be improved in the presence of adequate substrate delivery to the myocardium.

Another suggested mechanism for reduced myocardial responsiveness to adrenaline is that endotoxin may inhibit adenosine 5′-triphosphate (ATP)-dependent calcium uptake by the sarcoplasmic reticulum, which could depress the contraction process (Hess & Briggs, 1971). Shinebourne, Hess, White & Hamer (1969) reported that the effect of noradrenaline on myocardial contractility is directly related to the increased rate of calcium uptake by the sarcoplasmic reticulum. A similar linkage may have explained the increased inotropic responses of hearts administered endotoxin and treated with digoxin (Hinshaw *et al.*, 1973). Finally, decreases in pH have been implicated in explaining altered myocardial responsiveness to catecholamine stimulation (Thrower, Darby, Aldinger, Tenney & Westbrook, 1959; Darby, Aldinger, Gadsen & Thrower, 1960). In the present study, mean arterial pH values in both control and experimental groups ranged between 7.35 and 7.45, and there was no apparent correlation between responsiveness to adrenaline and pH in individual experiments.

The precise role of the sympathoadrenal system in shock is difficult to interpret. Depression of myocardial responsiveness to circulating catecholamines and sympathetic stimuli have been implicated in explaining decreased heart function in shock. On the other hand, excessive sympathoadrenal stimuli are known to elicit severe myocardial tissue damage (Palmerio *et al.*, 1962; Lundsgaard-Hansen, Meyer, Riedwyl & Zierrot, 1969). The relative adverse contributions of these influences on the pathogenesis of myocardial dysfunction in shock remain to be elucidated.

This research was supported by the USPHS NIH grant HL 15037, U.S. Navy Contract N00014-68-A-0496, the Oklahoma Heart Association, and the Veterans Administration Hospital. Appreciation is expressed to Beverly Beller, Jeanette Glasgow and R.T. Brantley for technical assistance.

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(Received October 15, 1974.
Revised December 24, 1974)