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PRECIPITATION OF CARDIAC FAILURE IN ENDOTOXIN SHOCK

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Introduction

The serious nature of bacteremic shock has been emphasized in a recent report which estimates that 70,000 deaths each year result from bacteremia due to gram-negative organisms (26). Recent publications in the clinical literature (4, 24, 40), and results from experimental studies (7, 20, 41) have implicated heart failure or myocardial depression in septic or endotoxin shock. Some have suggested that the myocardium fails only terminally while others point out that depression of cardiac function may occur during the intermediate stages of shock. Several investigators have provided data to suggest that the heart is relatively resistant to endotoxin or its released products, during the early or intermediate stages of shock (3, 15, 16, 17, 22, 29, 46). The heart has also been reported to be relatively resistant to the effects of hemorrhage by some investigators (8, 15, 19, 31) but susceptible to damage by others (2, 10, 20, 39). A complication in determining whether the heart fails as a pump, or if cardiac output falls because of peripheral pooling, is that venous return is reported to decrease in various animal species during the early phase of shock due to trapping of blood in peripheral tissues (18, 46). At the present time there is no available experimental data which evaluates the relative contributions of peripheral and cardiac factors in the intermediate stage of shock explaining the decrease in cardiac output.

The purpose of the present study is to attempt to provide a partial answer to this question by assaying myocardial performance during the intermediate phase of endotoxin shock. Results indicate that in contrast to previous work reported from this laboratory in which the heart performed normally during the early (0-4 hours) phase of shock, the present study

shows that varying degrees of myocardial failure are readily observable at later periods following endotoxin administration.

Methods

Experiments were conducted on adult mongrel dogs intravenously anesthetized with sodium pentobarbital, 30 mg/kg. The basic procedure included isolating a left ventricle and supporting it with arterial blood from a heparinized support animal as shown in Figure 1, and as previously reported (16, 17).

The control group consisted of support animals providing blood to isolated working hearts, without endotoxin administration in either animal. The experimental group was comprised of support animals not receiving endotoxin but supplying blood to isolated hearts transferred from animals injected with endotoxin 5-6 hours. Responses in this group varied greatly and a number of experimental hearts were in such a severe state of failure that epinephrine had to be infused during the study in order to complete the experiment. Eight experiments at 9 hours were studied and heart performances were compared to a group of 10 control hearts in which endotoxin was not administered. Endotoxin (E. coli, Difco, Detroit) was injected intravenously into heart dogs at a dosage (0.3-0.7 mg/kg) which caused death in approximately 45 per cent of the animals in 5-6 hours, and the studies with expiring animals were terminated prior to transfer of the hearts.

During the equilibration period of the control isolated heart (in which endotoxin was not administered), aortic pressure was adjusted to 100 mmHg and cardiac output was set at 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 physiologic ranges. The mean coronary arterial pressure (afterload) of the isolated heart was adjusted sequentially from 75-150 mmHg in order to assay the performance characteristics of the left ventricle. Pressures were changed by adjusting a screw clamp on the aortic outflow while cardiac output was maintained constant. Since coronary pressure was controlled, cardiac output and blood temperature were held constant and arterial and venous blood samples were taken, cardiac work performance and metabolic and hemodynamic parameters could be evaluated at each separate afterload (range, 100-150 mmHg). All parameters reported in the study were steady state values.

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. Blood temperatures in the heart were maintained relatively constant within each experimental group by appropriate adjustments of water bath and heating pad temperatures. 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.

Stroke work in gram-meters was calculated from the formula used by others (30):

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

where MAP = mean aortic pressure (mmHg); LVEDP = left ventricular end diastolic pressure (mmHg) 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 (32). 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 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 mmHg/sec (16).

Electrocardiograms were obtained by placing the ground lead into the moist tissue surrounding the trachea, Lead 1 into the left ventricular myocardium adjacent to the lower edge of the left atrium and Lead 2 into myocardium at the apex of the left ventricle.

Coronary blood flow averaged 115 cc/min/100 gms left ventricle (weighed at termination of the experiments), at the first 100 mmHg coronary pressure in the control hearts (N = 10). Oxygen uptake was assumed to be negligible in atria and right ventricle (bypassed) as was reported by others (33) and averaged 9.0 cc/min/100 gms left ventricle at the first 100 mmHg afterload in the controls (N = 10).

The mean body weights for heart donors in experimental and control groups were 5.7 and 5.1 kilograms respectively. The mean left ventricular weights of the experimental and control hearts were 28 and 35 gms respectively. The range of body weights of both experimental and control support animals was 18-25 kilograms.

Responses of the experimental hearts varied from no observable failure in a few instances and extensive failure in others. The most typical responses have been selected for comparison with the control experiments, and hemodynamic, work performance and metabolic characteristics have been evaluated.

Results

Figure 2 is a representative control experiment illustrating the influence of mean aortic pressure (afterload) on myocardial work performance, hemodynamics and metabolism. Left ventricular end diastolic pressure (LVEDP) remained relatively constant while coronary flow, dP/dT, power (work/sec), O_2 uptake and CO_2 production increased as functions of elevated aortic pressure (100-150 mmHg). This experiment required approximately two hours from the first to the final 100 mmHg value shown on the recording and illustrates the relative stability of the control preparation.

Figure 3 is a typical example of the responses of a failing heart 7-9 hours post-endotoxin administration. In contrast to control hearts, it was not possible to elevate mean aortic pressure to 150 mmHg without precipitating massive heart failure. Infusion of epinephrine, 1 microgram/min (1 ug/min), readily permitted the elevation of afterload to 150 mmHg, which also resulted in a marked increase in coronary blood flow and in heart rate. Elevations in coronary flow, dP/dT, power (work/sec), O_2 uptake and CO_2 production as functions of an increased afterload (100 to 125 mmHg), were in the normal range and indistinguishable from control hearts. LVEDP, however, was significantly elevated above the normal heart at all aortic pressures, even during epinephrine infusion.

Figure 4 represents another type of response in which it was possible to increase afterload to the desired level of 150 mmHg, with concurrent abnormal elevations in LVEDP from 8.5 to 12.0 mmHg. All other cardiac parameters were insignificantly different from the control preparations although LVEDP and dP/dT were notably changed in the direction of the mean controls during epinephrine infusion (2 ug/min).

Figure 5 illustrates the marked responsiveness of the coronary circulation to elevations in mean coronary (aortic) perfusion pressure. The mean (± SD) of the control group of hearts (N = 10) is designated by a dotted line (± SD). There were no significant differences in flow between control and experimental groups (p 0.05). Coronary blood flow increases nearly 300 per cent with a two-fold increase in perfusion pressure, thereby signifying a drop in coronary vascular resistance as a function of increased aortic pressure.

Figure 6 displays results of dP/dT measurements. The mean (± SD) of the control group shown by the dotted line (± SD, solid line) shows that dP/dT values from failing hearts fall within the control series. However, Figure 7 shows that LVEDP's were notably increased in most failing hearts, even those with epinephrine infusion (which markedly lowered them from the existing values). Two endotoxin-injected animals yielded hearts which failed to reveal failure even during the earlier stages of perfusion. Most hearts from endotoxin-treated dogs exhibited significantly elevated LVEDP's. Symbols marked with "e" were hearts totally failing unless epinephrine was continually infused (1-2 ug/min).

Heart rates were extremely variable and no dominant pattern was observed in the failing state (Figure 8). Increases in rate appeared to correlate with increases in coronary flow (Figure 5), although one experiment (e) demonstrated that a slow rate may be associated with a high coronary blood flow. Changes in mean power (work/sec; gm·meters/sec) are shown in Figure 9. The mean ± SD of control group illustrates that power increases notably when mean aortic pressure is elevated. No basic differences were regularly seen between power responses of the failing heart and the controls.

Figures 10 and 11 provide values for oxygen uptake and carbon dioxide production in failing and non-failing hearts as a function of mean aortic pressure (afterload). Mean values of controls (dashed line) (± SD) show that O_2 uptake and CO_2 production are approximately doubled with a 50% increase in mean aortic pressure. Values from failing hearts were not significantly increased above control but average values were somewhat greater.

Predictive factors were sought which hopefully would provide a diagnostic basis for predetermining heart failure prior to carrying out work performance curves in the isolated state. Table I provides data on mean systemic arterial pressure (MSAP), heart rate, pH, hematocrit and rectal temperature in heart donor animals, recorded approximately five hours post-endotoxin, shortly before transferring hearts to the perfusion system. No clearly distinguishable features between the two non-failing and six failing hearts were discernible from comparison of mean values.

Table II is a comparison of LVEDP and dP/dT values as a function of mean aortic pressure (afterload) in control and experiment heart studies. Results suggest that there is a relative depression of cardiac contractility in failing hearts, particularly when it is considered that dP/dT should be increased more at a given afterload when LVEDP also increases (25,44).

Discussion

One of the most difficult problems in the pathogenesis of experimental septic shock is the evaluation of myocardial function during later phases of shock, when arterial pressure and cardiac output have been altered for extended periods. The aim of the present study was to provide an animal model

with a dose of endotoxin which would seriously insult the animal but permit survival of at least half of the animals five hours after endotoxin administration.

In contrast to previous studies carried out in this laboratory which demonstrated normal cardiac function up to 3 hours post-endotoxin (16, 17), the present work clearly demonstrates the ready susceptibility of the heart to failure if the time of shock is extended to 7-9 hours. Heart failure, indicated by elevated left ventricular end diastolic pressure (LVEDP) and relatively depressed dP/dT values, particularly at elevated afterloads, were observed in six of eight experiments. The failure observed was generally profound and incapable of reversal. Epinephrine intervention was necessary in some instances to reverse elevated LVEDP's which had risen above 20 mmHg, but cessation of infusion led to abrupt failure. The serious degree of failure observed in most of the hearts was considered to be remarkable since during the period of isolation and perfusion, mean coronary perfusion pressure and cardiac output of each heart were in the normal range and blood was continually exchanged with a large control non-shocked animal. The net effect of these factors would be expected to assist myocardial function, however, in nearly all instances, heart failure was profoundly irreversible, even after an extended period of perfusion and epinephrine infusion.

Another observation in the failing heart was that the combined effects of increased mean aortic pressure (afterload) and LVEDP should have increased myocardial contractility (25, 44) but dP/dT values on the average increased less than expected in comparison to the control, non-shocked, heart preparations. Assuming that the inotropic state of the failing heart is constant, as mean aortic pressure (afterload) is increased, preload (LVEDP) also rises

and the resultant effect should be a rise in dP/dT greater than seen in the control hearts. Data from the present study therefore is consistent with the view that dP/dT decreases in the failing heart.

The present finding that oxygen uptake of the failing heart is unchanged from control hearts appears puzzling; however, studies of myocardial energy utilization in heart failure have yielded conflicting results: Oxygen consumption has been found to be unchanged from normal or slightly elevated (42). Since it appears that the failing hearts of the present study exhibit a decline in contractility as evidenced by a depressed dP/dT, it would appear that oxygen uptake might fall. That such was not the case may be explained on the basis of the interaction of opposing factors: An increase in LVEDP suggests an augmentation of myocardial wall tension which should increase oxygen consumption while the decrease in contractility should diminish oxygen uptake. The resulting assimilation of oxygen by myocardial tissue may therefore be increased, decreased, or remain unchanged (9).

Another difficult finding to comprehend was that neither arterial pressure, heart rate, pH or hematocrit were observed to be predictive factors in assaying cardiac function of the dog prior to heart removal. Results from these studies suggest that procedures for evaluating left ventricular myocardial integrity in the septic shock patient should include measurement of LVEDP with altered afterloads.

It is clear that extremely potent factors are influential in damaging the myocardium if sufficient time is permitted for their effects. These are not identified at present although certain possible mechanisms may have been involved in the pathogenesis. Adverse circulatory conditions may have played a role as has been suggested by reports of others (1, 3, 31, 33, 38, 39).

Defects in the autonomic regulation of the heart may have intervened either as a result of sympathetic-vagal imbalance (7, 13), a damaged CNS (5, 11, 14), or altered adrenergic circulating influences (13, 15, 23). Coronary vascular obstruction may have occurred with coagulation products lodged in capillaries (26); decreases in both oxygen and pH (11), the circulation of toxic or depressant substances (20, 21, 23, 28, 36, 37, 43, 45) or a primary cellular defect (47) may have been unleashed to irreversibly damage the myocardium.

Summary

Experiments have been carried out to assay cardiac function in the intermediate stage of endotoxin shock. Performance curves were conducted by altering afterload through a wide range in order to compare myocardial work performance, coronary hemodynamics and cardiac metabolism in both control and endotoxin shocked dogs. Results clearly demonstrate the elicitation of heart failure 7-9 hours after endotoxin, as revealed by markedly elevated LVEDP, decreased dP/dT and the necessity of using an inotropic agent to drive the tailing ventricle through the imposed afterload performance curve. The myocardial dysfunction was profound and generally irreversible although temporary restoration of function was demonstrated by infusion of a beta adrenergic stimulating agent. No single parameter was discovered or identified which would serve a prognostic value in predetermining cardiac function prior to testing the heart with work performance stresses. The cause of failure has been discussed.

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Table I. Measurements in Intact Heart Donor Animals Five Hours Post-Endotoxin*

Experiment No.	MSAP** (mmHg)	Heart Rate (min)	pH	Hematocrit	Rectal Temperature (°C)
Non-failing:					
1	112	130	7.30	38	40.3
2	125	140	7.36	31	40.0
Failing					
1	75	151	7.23	--	38.0
2	130	150	7.28	40	39.2
3	132	140	7.44	37	41.0
4	85	140	7.15	38	38.2
5	101	210	7.09	--	43.0
6	80	110	7.23	53	32.8

*Last values recorded before commencing surgery to transfer heart to perfusion system

**MSAP = Mean systemic arterial pressure

Table II. Effect of Alterations in Mean Aortic Pressure on Changes in LVEDP and dP/dT in Isolated Working Hearts. (Mean ± SE)

Experiment	Mean Aortic Pressure (mmHg)									
	75		100		125		150		75	
	LVEDP	dP/dT	LVEDP	dP/dT*	LVEDP	dP/dT*	LVEDP	dP/dT*	LVEDP	dP/dT*
Controls (No endotoxin) (N = 7)	3.1 (±0.6)	2303 (±325)	+3.4 (±0.7)	+723 (±148)	+3.5 (±0.8)	+1642 (±171)	+4.0 (±1.6)	+2521 (±286)	+2.8 (±0.6)	+320 (±3.2)
Experimentals										
Non-Failing (N = 2)	+4 (±0)	1967 (±2)	+5.3 (±0.3)	+672 (±232)	+4.8 (±0.3)	+1336 (±150)	+6.3 (±1.3)	+2497 (±205)	+4.8 (±0.3)	+276 (±112)
Failing** (N = 5)	+9.0 (±3.3)	2204 (±320)	+12.1 (±5.3)	+463 (±71)	+13.5 (±3.7)	+1030 (±107)	+10 (±2.5)	+2136 (±280)	+6.7 (±2.7)	+343 (±24.2)

*Change from values at 75 mmHg (second column)

**Includes hearts administered epinephrine