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Effects of Glucose or Insulin on Myocardial Performance in Endotoxin Shock[1] (39433)

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Myocardial dysfunction in endotoxin or septic shock has been observed in several species including dog (1, 2) and man (3, 4). The precise mechanism for the failure has eluded description although inadequate coronary perfusion has been implicated as a primary determinant (5), and substrate deficiency has been suggested or implied (6, 7). A direct toxic action of endotoxin on the myocardium seems to have been excluded (1, 2), and a proposed adverse effect of a circulating myocardial depressant factor (8) has not been confirmed (2).

Hypoglycemia has been documented to perform a significant role in the pathogenesis of endotoxin and septic shock in animals (9–13) and man (9, 14). Hypoinsulinemia has been reported in subhuman primate septic shock by Cryer's group (15) and Hinshaw *et al.* (16) and in low output human septic shock by Clowes *et al.* (17). Diabetic-like glucose tolerance responses have been observed in septic shock patients by Gump and others (18).

Recent reports have suggested prominent roles of glucose and insulin in improving cardiac output in shock (6, 7, 17). Weissler and others (19) have suggested that the effect of insulin on the hypoxic isolated perfused rat heart is to increase utilization of glucose. Clowes *et al.* (17) suspected that infused insulin exerted a possible direct beneficial action on the myocardium in septic shock. Hiatt *et al.* (20) found that massive doses of insulin (2400–7500 units) prolonged survival in dogs for 30 hr to 10 days after ligation of the circumflex branch of the left coronary artery, whereas nontreated control dogs died within 16 min. They proposed that insulin infusion suppressed premature ventricular contractions, ventricular tachycardia, and fibrillation and diminished myocardial injury and ischemia (20). Our recent work documented the development of severe hypoglycemia during the intermediate stages of endotoxin shock. Animals becoming markedly hypoglycemic (<35 mg%) died in shock, whereas those receiving intravenous infusions of 50% glucose survived (13).

It occurred to us that the progressively developing hypoglycemia might be related to the precipitation of myocardial dysfunction in endotoxin shock. The purpose of the present study was to evaluate this possibility and determine the relative roles of glucose and insulin in supporting cardiac function in shock. Results from this study suggest that both the development of myocardial dysfunction following endotoxin insult and its subsequent reversal by insulin occur independently from changes in blood glucose concentrations.

Methods. Description of isolated heart preparations. Experiments were carried out on 15 isolated working canine heart preparations exchanging blood with intact support animals, as previously described (1, 2). The right ventricle was bypassed following cannulation of the pulmonary artery, and coronary venous return was obtained from a large-bore cannula introduced into the right ventricle (1, 2). During an equilibrium period, arterial blood from the support animal was supplied to the test heart, with lungs inflated, and the preparation was stabilized at a mean aortic pressure of 100 mm Hg and a cardiac output of 76 ml/min/kg (based on the weight of the dog supplying the isolated heart). Coronary venous return and aortic

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outflow from the isolated heart were collected separately, measured volumetrically, and returned to the support animal (1, 2). Intraventricular pressures, including left ventricular end diastolic pressure (LVEDP) were monitored via pressure transducers connected to a plastic cannula penetrating the apex of the left ventricle. Mean aortic pressure, pulmonary blood flow, and blood temperature were maintained constant. Cardiac power (grams·meters/second) and maximum positive (+) and negative (−) dP/dt (millimeters of Hg/second) were calculated as previously reported (1, 2). Blood pressure in the support animal and various parameters in the isolated heart were continuously monitored on a Sanborn recorder. Afterload was varied periodically in order to evaluate myocardial performance.

Description of glucose and insulin studies. Arterial blood glucose was determined with a Beckman glucose analyzer possessing an accuracy of ±3 mg%. Insulin (Iletin, Eli Lilly and Company, Indianapolis, Ind.) was either infused into the left atrium of the isolated heart or administered to the support animal via the blood reservoir. Experiments were divided into three groups of five studies each and were composed of an initial group receiving an LD_{100} of *Escherichia coli* endotoxin (Difco, Detroit). Endotoxin was administered intravenously to the support dog and simultaneously to the isolated heart (based on the weight of the animal supplying the heart) via the pulmonary artery. Hypertonic glucose, 50%, was infused in some experiments into the reservoir receiving blood from the isolated heart, at rates sufficient to maintain the coronary arterial glucose concentration constant. A second series was conducted in which endotoxin was administered, and, following demonstration of myocardial failure, insulin was infused continuously into the left atrium of the isolated heart for the duration of the study.

A final group of experiments was performed to determine the effects of insulin infusion on nonfailing hearts not treated with endotoxin. Insulin was infused into the left atrium at rates sufficient to sustain significantly improved myocardial performance, as indicated by decreased LVEDP and elevated dP/dt values. In approximately 1 hr following steady-state effects of insulin on heart performance, insulin infusion was stopped, the support dog was removed from the perfusion system, isolated lungs were ventilated with 20% O_2 and 5% CO_2, and the heart was monitored for approximately 1 hr. Insulin blood values in the isolated perfusion system were determined by radioimmunoassay (Phadebas insulin test, Pharmacia, Uppsala, Sweden).

Statistics were carried out utilizing a Student's t test.

Results. Table I presents results from five isolated perfused working left ventricles exchanging blood with intact support dogs. Following establishment of baseline heart performance values, an LD_{100} of endotoxin was administered to both heart and dog, and the arterial concentration of blood glucose reaching the heart was maintained constant by infusion of 50% glucose into the venous reservoir. Amounts of glucose infused varied greatly; however, the maximum decrease in glucose values from the control in all experiments did not exceed 4%. Results from individual heart studies shown in Table I demonstrate myocardial failure 3–4 hr postendotoxin: LVEDP rises significantly in each heart, and in heart No. 5, afterload could not be elevated above 50 mm Hg without induction of irreversible failure. Power values diminished from control in all instances while coronary blood flows were elevated in most hearts. Changes in positive and negative dP/dt and heart rate were variable. These results demonstrated that myocardial dysfunction after endotoxin may occur independently of arterial blood glucose concentrations, hypoglycemia being excluded, therefore, as a prerequisite for failure. The degree and time course of failure seen in the present series agrees with previously published reports (1, 2) on dogs subjected to endotoxin shock without glucose administration.

Table II illustrates results from a second series of five hearts receiving endotoxin as in Table I but additionally infused with insulin following the first significant indication of cardiac dysfunction as verified by imposed afterload stresses. The average time for demonstration of dysfunction was 3.4 hr postendotoxin as evidenced by significant

TABLE I. EFFECTS OF ENDOTOXIN ON MYOCARDIAL PERFORMANCE DURING GLUCOSE INFUSION[a]

Experiment	LVEDP[b] (mm Hg)		PE (hr)	Power (g·m/sec)		Coronary blood flow (ml/min/100 g)		+dP/dt (mm Hg/sec)		−dP/dt (mm Hg/sec)		Heart rate (min)	
	C	PE		C	PE	C	PE	C	PE	C	PE	C	PE
1	9.5	26.5	3	9.3	7.6	151	196	1613	1592	1645	1603	126	138
2	2.0	10.0	3	7.0	6.4	107	125	1923	1887	2632	2083	144	138
3	4.0	14.0	4	9.9	9.0	130	130	1851	1612	2173	2083	150	156
4	0.5	5.0	3	8.1	7.8	62	120	2000	1786	2778	2273	120	120
Mean ±SE	4.0 (2.0)	13.9 (4.6)		8.6 (0.6)	7.7 (0.5)	112 (19)	142 (18)	1847 (84)	1719 (71)	2307 (256)	2011 (143)	135 (7)	138 (7)
p Value	0.025												
5	4.0	17.5	4	4.3	3.1	69	96	862	922	1063	1136	120	114

[a] Infusion of 50% glucose at a rate sufficient to maintain arterial blood concentration constant. Expt 1–4 at afterload of 100 mm Hg; expt 5 at afterload of 50 mm Hg.
[b] LVEDP = left ventricular end diastolic pressure; C = control; PE = postendotoxin.

increases in LVEDP and depressions in power and $-dP/dt$ at 100 or 125 mm Hg afterloads. Mean glucose values declined, though insignificantly, during the postendotoxin period. Insulin administration was found to exert a beneficial action on myocardial performance: Infusion, which continued during the 3–5-hr period after endotoxin, was adjusted on the basis of achieving end diastolic pressures at control values or lower. Results demonstrate mean decreases in LVEDP at afterloads of both 100 and 125 mm Hg, within 2 hr of infusion, the most marked mean reduction, 17.1 to 4.3 mm Hg, occurring by the fourth hour at an afterload of 125 mm Hg. Coronary blood flow was increased and $+dP/dt$ was elevated at 100 mm Hg ($p \leq 0.025$). Changes in power, $-dP/dt$, and heart rate were insignificant in comparison with control values. Glucose concentration progressively fell during the postendotoxin course, reaching values of 43 and 33 mg% ($p < 0.05$) at afterloads of 100 and 125 mm Hg, respectively. These results demonstrated reversal of dysfunction by insulin infusion and sustained improvement of myocardial function during subsequent periods of hypoglycemia. Favorable effects of insulin were observed following its termination of infusion. Results from one experiment demonstrate its duration of action: Three hours following endotoxin administration, LVEDP rose from 3.0 to 22.5 mm Hg at an afterload of 125 mm Hg. Approximately 80 U of insulin was then infused during a period of 1.5 hr, resulting in a drop of LVEDP to 3.5 mm Hg. Insulin infusion was then terminated, and 50 min later LVEDP remained stabilized at 3.5 mm Hg at an afterload of 125 mm Hg.

The effects of insulin infusion on isolated hearts not receiving endotoxin are displayed in Table III. The first period of heart performance is 1–3 hr following onset of insulin administration, when the support dog is in the perfusion circuit (as in the previous series). The second and third periods of 3–4 hr represent the periods during which the heart was totally separated from the support animal so that there was no source of bloodborne agents. Results show notable decreases in LVEDP at 100 and 150 mm Hg

TABLE II. EFFECTS OF INSULIN ON MYOCARDIAL PERFORMANCE IN ENDOTOXIN SHOCK[a]

Parameter	Control	Postendotoxin (mean, 3 hr)	Postinsulin (mean, 4 hr postendotoxin)	Postinsulin (mean, 5 hr postendotoxin)
Afterload, 100 mm Hg				
LVEDP (mm Hg)	4.9	9.3 (p, 0.02)	9.8	3.5
Power (g·m/sec)	11.2	10.6 (p, 0.01)	10.4	10.6
Coronary blood flow[b]	81	99	104 (p, 0.025)	120 (p, 0.02)
$+dP/dt$ (mm Hg/sec)	2132	2251	2293	3137 (p, 0.02)
$-dP/dt$ (mm Hg/sec)	2716	2028	2363	2771
Heart rate (min)	142	151	154	152
Glucose (mg%)	121	99	89	43 (p, 0.001)
Afterload, 125 mm Hg				
LVEDP	6.6	17.1 (p, 0.05)	4.3 (p, 0.05)	4.3
Power	13.9	12.4	14.2	14.2
Coronary blood flow[b]	100	117 (p, 0.05)	124	142
$+dP/dt$	2725	2230	2572	2997
$-dP/dt$	3302	2018 (p, 0.05)	2753	2929
Heart rate	146	150	146	149
Glucose	118	98	70	33 (p, 0.05)

[a] Data from five isolated canine heart preparations maintained at constant cardiac output and afterloads of 100 mm Hg (performance evaluated at 125 mm Hg). Blood is exchanged with intact animal. Ranges of insulin infused, 70-5500 units. Statistical significance compared to controls.
[b] Milliliters per minute per 100 g, left ventricle.

TABLE III. EFFECTS OF INSULIN ON MYOCARDIAL PERFORMANCE IN THE ABSENCE OF ENDOTOXIN[a]

Parameter	Control	Postinsulin (1-3 hr) (dog in circuit with heart)	Postinsulin (3.5 hr) (Heart isolated, dog removed)	Postinsulin (4.0 hr) (Heart isolated, dog removed)
Afterload, 100 mm Hg				
LVEDP (mm Hg)	2.7	0.7 (p, 0.02)	1.3 (p, 0.05)	1.4 (p, 0.02)
Power (g·m/sec)	9.3	9.5	9.4	9.4
Coronary blood flow[b]	103	118	114	114
$+dP/dt$ (mm Hg/sec)	2024	3321 (p, 0.001)	2970	2636 (p, 0.02)
$-dP/dt$ (mm Hg/sec)	2682	3448 (p, 0.01)	2983	2855
Heart rate (min)	140	154 (p, 0.05)	111 (p, 0.01)	104 (p, 0.001)
Glucose (mg%)	127	46 (p, 0.001)	28 (p, 0.001)	16 (p, 0.001)
Insulin infused (units)		7900	100	0
Afterload, 150 mm Hg				
LVEDP	4.5	1.4 (p, 0.02)	2.1	2.9
Power	14.0	14.2 (p, 0.05)	14.5	14.6
Coronary blood flow[b]	166	195	168	181
$+dP/dt$	2880	4936 (p, 0.005)	4113 (p, 0.025)	3983 (p, 0.05)
$-dP/dt$	3466	5020 (p, 0.02)	3895	4123 (p, 0.05)
Heart rate (min)	147	161 (p, 0.01)	114 (p, 0.025)	106 (p, 0.005)

[a] Data from five isolated canine heart preparations, receiving infusions of insulin without endotoxin. Statistical significances compared to control values.
[b] Milliliters per minute per 100 g, left ventricle.

afterloads ($p < 0.05$) within 3 hr after onset of insulin administration. Mean $+dP/dt$ increased while the arterial glucose level fell to 46 mg% ($p < 0.001$) within 3 hr of insulin infusion at an afterload of 100 mm Hg. During the same period, elevations of power, $+dP/dt$, and $-dP/dt$ were seen at 150 mm Hg ($p \leq 0.05$). Glucose values in arterial blood continued to fall after removal of the support animal from the heart perfusion system, reaching concentrations of 28 mg% at 3.5 hr and 16 mg% at 4.0 hr while LVEDP, power, coronary blood flow, $+dP/dt$, and $-dP/dt$ remained at control values or were improved above control values ($+dP/dt$, $p = 0.02$, at 100 mm Hg

afterload and $+dP/dt$, $p = 0.025$, and $-dP/dt$, $p = 0.05$, at 150 mm Hg afterload). Insulin concentrations in the reservoir at the end of each experiment were in excess of 320 μU/ml. These observations suggest that insulin infusion exerts a profoundly beneficial effect on myocardial performance which is sustained for long, steady-state periods and occurs in spite of extreme hypoglycemia.

Discussion. The purpose of this report was to determine if the hypoglycemia of endotoxin shock bore a causal relationship to the elicitation of myocardial dysfunction. Previous work in this laboratory documented progressively developing cardiac failure (1) and lethal hypoglycemia (13) after endotoxin in the dog. It seemed reasonable that some connection might exist between the two pathophysiological phenomena. Administration of hypertonic glucose has been reported to elicit beneficial myocardial responses and elevations of cardiac output. Baue *et al.* (21) and Replogle and others (22) administered 50% glucose to dogs in shock and reported increases in cardiac output. Beneficial effects of glucose in critically ill patients have been reported by Pindyck's group (6) who observed increases in cardiac output and left ventricular stroke work with hypertonic glucose. These above observations, including the reported hypoglycemia in canine endotoxin shock, the survival benefits of infused glucose (9, 13) in endotoxin shock, and recent reports of hypoglycemia in septic shock patients (9, 14), strongly suggest that elevated blood glucose concentrations should augment myocardial performance. Results from the present study, however, fail to confirm this possibility: Severe myocardial dysfunction occurred at all levels of glucose concentrations (5–125 mg%), and maintenance of glucose at control or higher levels by infusion was without benefit to the myocardium. These findings suggest that the reported beneficial effects of infusion of hypertonic glucose may be due to peripheral rather than direct, cardiac actions. The observed increase in cardiac output by Replogle's group (22) and maintenance of mean arterial pressure in dogs shocked with endotoxin (13) may be due to augmented venous return and improved metabolic status following hypertonic glucose infusion.

Of particular interest in the present study were the significant beneficial cardiac effects of insulin in both failing and normal hearts. Very recently Weisul's group (7) demonstrated the effectiveness of an infusion of glucose, insulin, and potassium in clinical septic shock. They confirmed the presence of severe myocardial depression in low cardiac output septic shock and although isoproterenol improved performance it did not correct the depression of cardiac function. On the other hand, a solution of glucose, insulin, and potassium dramatically improved performance and corrected myocardial abnormalities (7). Weissler *et al.* (19) described the beneficial effects of insulin on the performance of the hypoxic isolated perfused rat heart and ascribed its benefit to the increased myocardial utilization of glucose. Weisul *et al.* (7) could not describe the mechanism of action of the solution of glucose, potassium, and insulin in their septic shock patients but suggested that it was linked to the prevention of both loss of potassium and gain of sodium in myocardial tissue, thus supporting the transmembrane action potential and myocardial contractility. Clowes and others (17) were also unable to explain the mechanism by which cardiac function is improved by glucose, potassium, and insulin in septic shock but suggested that glucose transport and glycolysis were enhanced and that the cell membrane potential was restored. Results from the present study indicate that insulin infusion alone clearly improves myocardial performance of the failing heart in endotoxin shock. Further, its strong inotropic influence did not depend on existing blood glucose levels, as was also observed in normal hearts not administered endotoxin. This observation is consistent with the view that insulin possesses a direct myocardial action, since normal hearts, which would not be expected to possess metabolic defects or altered transmembrane potentials, responded in a fashion similar to failing hearts. Of importance is the observation that severe hypoinsulinemia is consistently observed in subhuman septic shock (15, 16) and in patients with low output septic shock (17).

Since depressed heart function has been demonstrated in human septic shock (3, 4), the beneficial actions of infused insulin may be due in part to its important influences on myocardial contractility. Currently conducted isolated heart studies reveal an increase in heart rate from 158 to 169 beats/min ($p < 0.005$) at low doses of glucagon infusion (1 μg/min), and, since heart rates were unchanged after insulin in the present study, glucagon as an impurity in the insulin solution does not appear to be the agent mediating improvement of myocardial performance.

Summary. Past studies reported by this laboratory have documented myocardial dysfunction and progressively developing hypoglycemia in canine endotoxin shock. The purpose of the present study was to determine the effects of glucose concentrations and insulin infusions on myocardial performance following endotoxin administration. Experiments were carried out on isolated, working canine left ventricular heart preparations exchanging blood with intact dogs. Myocardial function was evaluated following endotoxin and correlated with concentrations of glucose and effects of insulin infusion. Cardiac dysfunction occurred within 2–4 hr postendotoxin and the degree of malfunction was not related to arterial blood glucose concentrations. Maintaining blood glucose at control, preshock, levels by infusion of 50% glucose did not prevent myocardial dysfunction as evidenced by elevations of left ventricular end diastolic pressure, and depressed power. Infusions of insulin reversed cardiac failure and maintained normal performance in spite of wide ranges in glucose concentration (5–120 mg%). Findings suggest that myocardial dysfunction is not precipitated or enhanced by the hypoglycemia of endotoxin shock. The beneficial actions of infused insulin on cardiac performance appear to be elicited on the basis of mechanisms other than myocardial glucose transport.

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