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Evidence for a Beneficial Effect of Intravenous Glucose on the Hemodynamic Response to Acute Asphyxia[1] (38622)

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Glucose therapy for acute myocardial infarction was first advocated over a decade ago (1), but after extensive clinical trials its success in reducing patient mortality has remained in doubt (2, 3). However, an impetus to continue these trials has recently been provided from a study in the dog in which infarct size was shown to be significantly reduced when administration of glucose was began promptly after coronary vessel occlusion (4). This recent validation of a positive myocardial effect of intravenous glucose therapy in the intact animal suggests that such therapy might be effective in improving myocardial function after a hypoxic insult to the heart from causes other than acute myocardial infarction. Previous *in vitro* studies have shown that glucose reduces the negative inotropic effect of acute hypoxia on cardiac muscle (5–8) and an *in vivo* study in the dog revealed that glucose loading the heart aided its performance after 30 min of total cardiopulmonary by-pass without coronary flow (9). The purpose of the present study was to determine whether the intravenous administration of isotonic glucose to an intact animal recovering from acute asphyxia would alter the hemodynamic response of the animal to a second asphyxic stress.

Methods. Experiments were performed on 24 New Zealand white rabbits with a weight range of 3.3–4.6 kg. The animals were gently restrained, and after the local injection of 2% lidocaine the femoral artery and vein on each side were cannulated. General anesthesia was achieved with sodium pentobarbital, 30 mg/kg, iv. The initial anesthetic dose was given by constant venous infusion over a 10- to 15-min period to minimize heart rate and blood pressure alterations. After this initial dose, a maintenance dose equal to 10% of the original dose per hour was infused during the remainder of the experiment. Rectal temperature was monitored and a heating pad placed beneath the animal was adjusted to maintain body temperature constant. A venous infusion of 6% Dextran 70 (McGraw) was adjusted throughout the experiment to replace the volume of blood withdrawn or lost by hemorrhage. The trachea was intubated and respiration was maintained with a small-animal respirator (Harvard Apparatus, model 661). Arterial blood pressure was monitored utilizing a Statham strain gauge (P23Db). Needle electrodes were used to obtain an electrocardiogram.

The experimental protocol consisted of exposing the animals to two 4-min asphyxic stress periods with a 15-min recovery period intervening. The protocol during the two stress periods was identical. The stress was induced by switching the respirator to recycle the same respired air for 4 min. During the preparation and the recovery period the animal was respired with room air. Arterial blood samples were collected just prior to each stress for control values. Samples were then drawn at 1-min intervals throughout each stress. One sample was also taken at the midpoint, that is, the 7-½-min point, of the recovery period. All of the samples were analyzed for arterial blood PO_2, PCO_2, and pH (Instrumentation Laboratories, model 113). The control samples, the 4-min samples taken at the end of each stress, and the recovery period samples were also analyzed for hematocrit and for whole blood lactate and glucose (10). The hemodynamic variables measured were systolic, diastolic, and mean blood pressure and heart rate. During the 15-min recovery period an isotonic solution of either glucose or a nonmetabolizable hexose, mannitol, was infused into randomly chosen animals. In each case the amount infused was equal to 40% of the animals total body glucose

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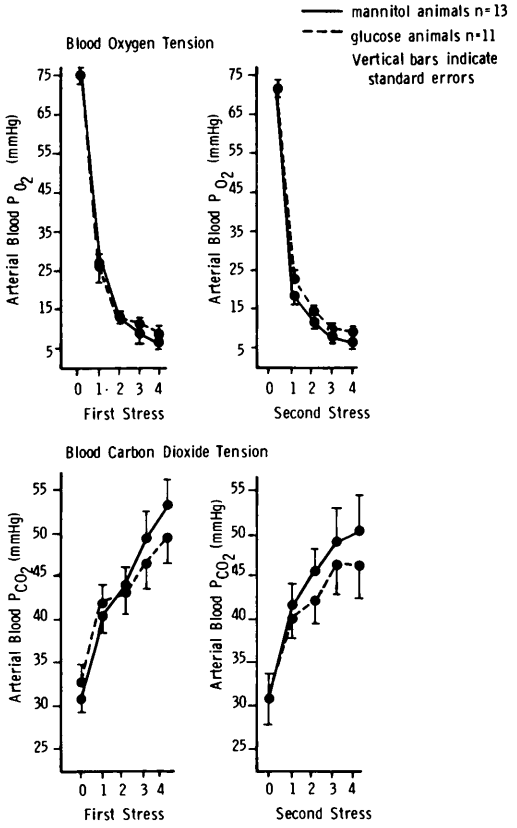

FIG. 1. Arterial blood gas (PO_2 and PCO_2) changes during the first and second stress in the control (solid line) and the experimental (dashed line) groups.

space. By this method a physiologic range of glucose levels was attained, in contrast to the extremely high glucose levels which are characteristically used during *in vitro* investigations. The control group was composed of the 13 animals that received isotonic mannitol. The experimental group consisted of the 11 animals that received isotonic glucose.

The Wilcoxon Matched Pairs Signed Ranks Test (11) was used to determine whether the responses occurring during the second stress period were significantly different from the responses of the first stress period in the same group. The Mann–Whitney *U* Test (12) was used to compare the two groups to determine whether glucose had any effect on the responses occurring during the second stress period.

Results. The method used to induce changes in the blood gas levels produced a marked hypoxemia and hypercapnia (Fig. 1). Comparison of the blood gas changes of the control and the experimental group showed no significant difference at any of the measured points. These data indicate that the induced stresses were consistent and reproducible. PO_2 and PCO_2 values obtained at the midpoint of the recovery period were at the control level.

The whole blood glucose values of the control and the experimental groups at the beginning of the first stress were not different (Fig. 2). There was a significant increase in blood glucose during the recovery period in both the control and the experimental group. Statistical analysis showed that the rate of increase in the early recovery period was significantly greater in the group receiving glucose than in the control group. The increase that occurred in the control group is evidence for a catecholamine effect on the liver during the recovery period. The blood glucose level of both groups declined during the stress periods. Comparison of the two groups showed no difference in this decrease.

The left side of Fig. 3 shows the systolic blood pressure response of the control animals to the first and second stress. While the pattern of blood pressure responses during the two stresses was similar, the magnitude of the changes differed significantly. The blood pressure declined more rapidly and fell to much lower levels during the second stress. This accentuated fall in systolic pressure, first noted at 60 sec, became greater as the second stress progressed.

The right side of Fig. 3 shows the systolic blood pressure performance of the experimental group. Comparison of the control and experimental animals first stress pressures revealed no significant differences. In contrast to the control group, the systolic pressure changes of the experimental animals during the second stress were not significantly different from the corresponding first stress pressures at any time. Thus the greater fall in systolic pressure which occurred during the second stress in the control group was completely prevented by glucose infusion in the experimental group. An intergroup statistical evaluation of the

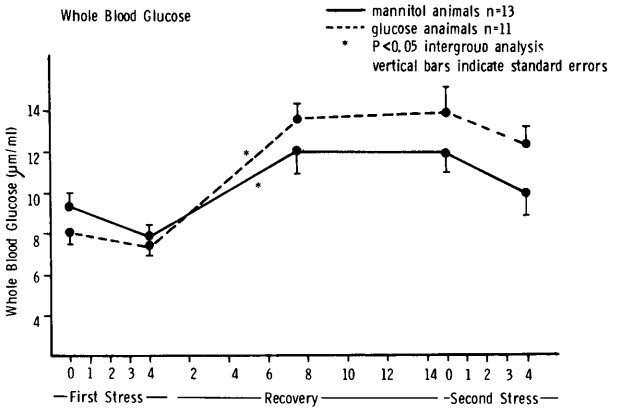

FIG. 2. Whole blood glucose changes in the control (solid line) and the experimental (dashed line) groups during each stress and the recovery period.

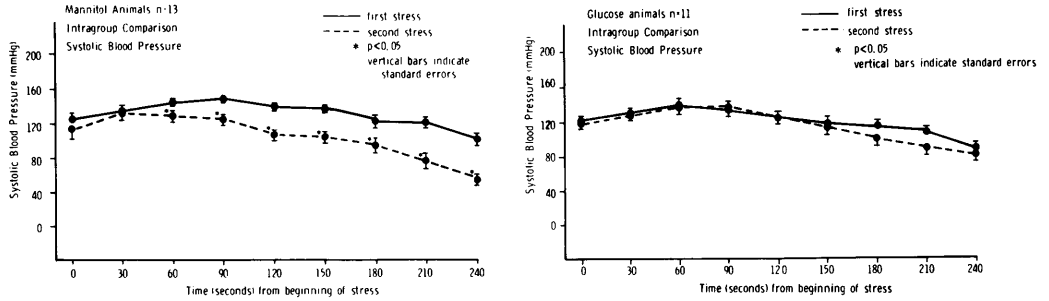

FIG. 3. Systolic blood pressure values of the control (left side of the figure) and the experimental (right side of the figure) groups during the first (solid line) and the second (dashed line) stress.

first to second stress systolic blood pressure differences is shown in Fig. 4. By the 1-min point the systolic pressure difference of the control group was significantly greater than the corresponding difference in the experimental group. Once established this statistical difference continued, except at the 180-sec point, to the end of the stress.

As seen in Table I, the diastolic pressure of both groups of animals fell more rapidly during the second stress than during the first stress. There was no significant difference between the control group and the experimental group in the diastolic pressure changes.

Examination of the heart rate data in both groups of animals revealed a bradycardia during each stress period (Table I). Comparison of the two groups revealed no significant difference in the pattern of heart rate responses.

There was a statistical increase in whole blood lactate during each stress period in both the experimental and the control group (Table I). Comparison of the blood lactate of the experimental and the control group did not reveal any significant differences.

Arterial pH decreased during each stress period (Table I). There was no difference between the two groups in their pH changes.

Discussion. Increased reliance on anaerobic metabolism is an integral part of the response of the myocardium to asphyxia. The capacity for anaerobic metabolism is in turn dependent on the availability of the carbohydrate substrates, glycogen and glucose. With the present experimental design, animals were exposed to a severe hypoxemic stress before either glucose or a nonmetabolizable hexose was administered. The debilitation caused by this first stress increased the sensitivity of the test for an effect of glucose on the animals' responses to hypoxemia. This test was conducted with

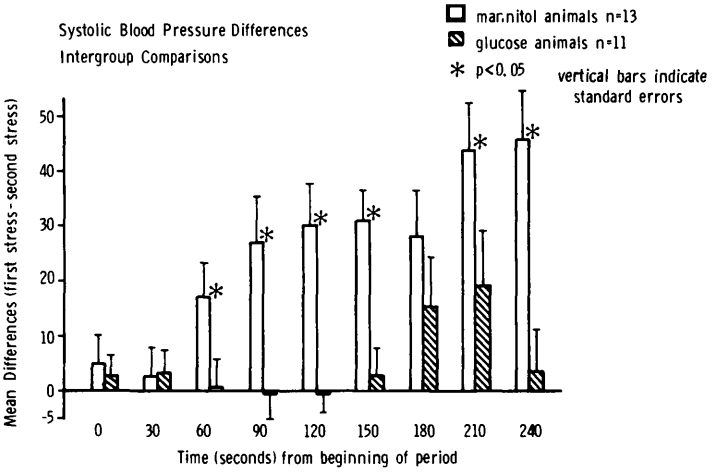

FIG. 4. Comparison of the control (open bars) and the experimental (diagonally lined bars) groups systolic blood pressure differences during the 4-min stress periods.

TABLE I. INITIAL, 2-MINUTE AND 4-MINUTE STRESS PERIOD VALUES OF THE CONTROL AND EXPERIMENTAL GROUPS FOR BLOOD PRESSURE, HEART RATE, ARTERIAL BLOOD pH, AND WHOLE BLOOD LACTATE

	Control (Sec)			Experimental (Sec)		
	0	120	240	0	120	243
Systolic pressure (mmHg)						
1st stress	122.4	136.7	97.4	124.4	128.4	89.0
	±2.6	±4.1	±6.4	±4.4	±6.5	±4.2
2nd stress	109.5	105.6	51.7	122.2	128.6	83.3
	±9.5	±6.2	±6.8	±2.7	±5.7	±7.5
Diastolic pressure (mmHg)						
1st stress	73.5	81.5	54.5	83.19	84.55	59.54
	±2.9	±3.6	±6.1	±5.31	±5.73	±6.09
2nd stress	74.9	63.5	18.5	75.46	74.82	23.82
	±3.6	±4.0	±4.9	±4.17	±3.89	±5.72
Heart rate (beats/minute)						
1st stress	261.5	193.8	149.2	272.7	176.4	165.4
	±9.7	±14.2	±11.0	±10.2	±10.7	±23.9
2nd stress	270.0	216.9	125.4	278.2	212.7	143.6
	±10.5	±13.4	±10.5	±11.6	±18.2	±13.4
pH						
1st stress	7.56	7.43	7.33	7.55	7.42	7.35
	±0.024	±0.191	±0.014	±0.021	±0.016	±0.015
2nd stress	7.52	7.38	7.31	7.49	7.40	7.32
	±0.168	±0.026	±0.013	±0.015	±0.016	±0.016
Lactate (μm/ml)						
1st stress	2.45		4.427	2.14		3.83
	±0.311		±0.263	±0.339		±0.313
2nd stress	4.78		5.53	4.30		5.32
	±0.408		±0.390	±0.544		±0.599

intact animals that possessed relatively normal circulatory, nervous and endocrine system interactions. The increased sensitivity of the present approach coupled with the physiologic animal model permitted a more satisfactory evaluation of the effects of glucose than has been possible with previous studies.

The results demonstrated that the infusion of isotonic glucose during the recovery period after the first asphyxic stress had a significant effect on systolic blood pressure during the subsequent asphyxic stress. The physiologic status of the animals at the beginning of the second stress depended on both the length of the recovery period and the repletion or repair processes that occurred during this time. It has been demonstrated that elevated levels of cardiac glycogen enhance myocardial performance during periods of hypoxia (13–15). In the present study the glucose infusion could have allowed a more rapid and complete restoration of cardiac glycogen stores thereby returning the experimental animals closer to their pre-first stress physiologic state. It has been shown that after an anoxic stress it requires 20 min for glycogen stores in the rat myocardium to return to 50% of the original level (16). As a 15-min recovery period was used in the present experiments, any action facilitating such repletion would have a beneficial effect. In addition, the rapid glucose loading of the experimental animals early in the recovery period may have limited the injury initiated during the first stress. Thus, the salutary effect of glucose could be due to a direct effect on the myocardium to maintain cellular viability and provide energy for the contractile mechanism.

Other possible sites of action of the intravenous glucose should be considered. Systolic pressure could have been maintained through an alteration in venous return due to an effect of glucose on venous compliance, or glucose could have acted on the arterial system to maintain arteriolar tone. Against this, however, is the fact that the diastolic blood pressure, which more closely reflects the state of peripheral resistance than systolic pressure, was not different in the two groups. A final consideration is that neural reflex and humoral support of myocardial function could have been enhanced in the experimental group by an action of glucose on afferent or efferent components of the autonomic or central nervous system. Further studies are needed to fully elucidate the mechanisms involved in the effects seen in the present study.

It is now clear that in the intact animal glucose can significantly modify the hemodynamic changes which occur during acute asphyxia. The results of the present study support the rationale for glucose therapy after an asphyxic insult to the heart.

Summary. Anesthetized rabbits were subjected to two 4-min periods of asphyxia with a 15-min recovery period intervening. During the recovery period animals received an iv infusion of either isotonic glucose or mannitol. Results indicated that glucose had a beneficial effect on systolic blood pressure during the second period of asphyxia. A direct metabolic action of glucose on the myocardium is favored as the explanation, but other possibilities include peripheral or neurohumoral effects.

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