Glucose Intolerance During Decreased Physical Activity in Man

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SUMMARY

Impaired glucose tolerance is a well documented consequence of absolute bedrest in man. Previous studies have shown a decrease in forearm glucose uptake during intravenous glucose infusion after fourteen days of bedrest. Bedrest is associated not only with physical inactivity but with a change in gravitational vector. This study was designed to examine the individual contributions of these factors to the glucose intolerance of bedrest. Thus, glucose tolerance tests were carried out in exercising subjects at bedrest and in rhesus monkeys immobilized in the vertical plane. Exercise in man improved glucose tolerance during bedrest, and vertically immobilized monkeys demonstrated significant glucose intolerance. It is concluded that the glucose intolerance of bedrest is a function of the decrease in physical activity. DIABETES *21*:101-07, February, 1972.

Over twenty years ago diminished glucose tolerance was noted in man during decreased physical activity; yet, only recently has this aspect of carbohydrate metabolism been studied in depth. In 1959 Lutwak and Whedon[1] reported abnormal intravenous glucose tolerance tests after one to three weeks of bedrest in normal subjects. Recently, Pawlson et al.[2] demonstrated significant glucose intolerance and hyperinsulinemia following oral glucose loads after twelve days of bedrest. Previous studies from this laboratory suggest that the impairment in forearm glucose uptake after fourteen days of absolute bedrest in man[3,4] was related to peripheral insensitivity to endogenous insulin. Since the subjects of these studies were maintained both at rest and in a horizontal position, the individual contributions of physical inactivity and diminished gravitational stress could not be distinguished. Accordingly, the present study was undertaken in an attempt to define the relationship of these factors to the glucose intolerance of bedrest. The experimental design included the effects of immobilization in both the erect and supine position with and without physical activity.

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MATERIALS AND METHODS

Twenty-three healthy young men between the ages of eighteen and twenty years were studied. All were volunteers who consented to the study after having been informed of the potential hazards and complications. Each had a negative family history of diabetes mellitus and a normal standard oral glucose tolerance test. All were within 10 per cent of their ideal weight and were fed a constant, freeze-dehydrated diet consisting of 2600 cal. and 260 gm. of carbohydrate. Glucose concentrations were determined in duplicate by the potassium ferricyanide-ferrocyanide method on a Technicon AutoAnalyzer.[5] Serum immunoreactive insulin determinations were done in duplicate by a modification of the method of Herbert et al.[6] Significance of mean differences was tested by the Student *t*-test and probabilities at the 5 per cent level or less were accepted as significant.

Forearm glucose uptake following three days of absolute bedrest and following fourteen days of limited activity

Seven subjects were used in this study, which was divided into (a) a two week pre-bedrest control period

of normal, but unregulated activity, (b) three days of absolute bedrest during which time the subjects were confined to bed and not permitted more than twenty degrees of head elevation followed in one month by (c) fourteen days of limited activity during which time the subjects were permitted three hours of quiet standing without exercise per day while the remaining twenty-one hours were spent at absolute bedrest. Glucose infusions were performed after an overnight fast according to a previously described method.[4] In brief, arteriovenous glucose differences, forearm blood flow and peripheral glucose uptakes were determined prior to and during a 180-min. continuous glucose infusion. The glucose infusion rates required to produce the glucose concentration curves in the control period were duplicated for each individual during the subsequent bedrest and limited activity infusions by adjusting the rate of glucose infusion. Venous glucose concentrations were monitored continuously by introducing venous blood from a catheter in a brachial vein into an AutoAnalyzer. Urinary glucose was determined by a gas chromatographic technic and blood flow through the forearm was determined by a plethysmographic method.[7]

Oral glucose tolerance tests in subjects during prolonged bedrest: Effect of exercise on glucose tolerance

The study consisted of a six week pre-bedrest control period followed by a thirty-five-day period of absolute bedrest. During the control period all eight of the subjects participated in an exercise program using a specifically designed body ergometer that permitted vigorous exercise in the supine position. Each subject spent one hour per day divided into three twenty-minute periods exercising to 70 per cent of his maximum oxygen consumption and performing 300,000 ft.-lb. of work per day. The total energy expended was 600 Kcal. per day as determined by oxygen consumption. The mean heart rate throughout the exercise period was 150 beats per minute. During the bedrest period four of the eight subjects were confined to bed while continuing the identical exercise program while the other four remained confined to bed without the exercise. Oral glucose tolerance tests were performed on the fortieth day of the control period and on the thirty-fifth day of the bedrest period.

Intravenous insulin tolerance tests before and after fourteen days of bedrest

Eight male volunteers participated in this study which was divided into a control period of two weeks of normal activity followed by a period of absolute bedrest for fourteen days. Intravenous insulin tolerance tests were carried out in the forenoon fasting state during the control period and on the fourteenth day of absolute bedrest.

Intravenous glucose tolerance tests in normal and vertically immobilized rhesus monkeys

Fifteen male rhesus monkeys (*Macaca mulatta*) ranging in weight from 3.4 kg. to 6.8 kg. were maintained on an ad libitum standard diet of monkey chow. After three days of carbohydrate loading consisting of 50 gm. of glucose per day, ten normal monkeys underwent an intravenous glucose tolerance test using 1 gm. of glucose per kg. body weight. Five other monkeys were immobilized in the vertical position according to the following method: All of the monkeys were anesthetized with Sernylan (1 mg./kg. body weight) during the construction of full body casts according to the method of Kazarian and Von Gierke.[8] After construction of the casts, the monkeys were placed in the vertical position. These animals were fed similar diets as the controls twice daily by hand. After two to sixteen weeks of immobilization and following three days of carbohydrate loading, intravenous glucose tolerance tests were performed on these monkeys. The glucose disappearance rate was calculated according to the method of Lundbaek.[9]

RESULTS

Forearm glucose uptake during bedrest and limited activity

There was no consistent weight change during the

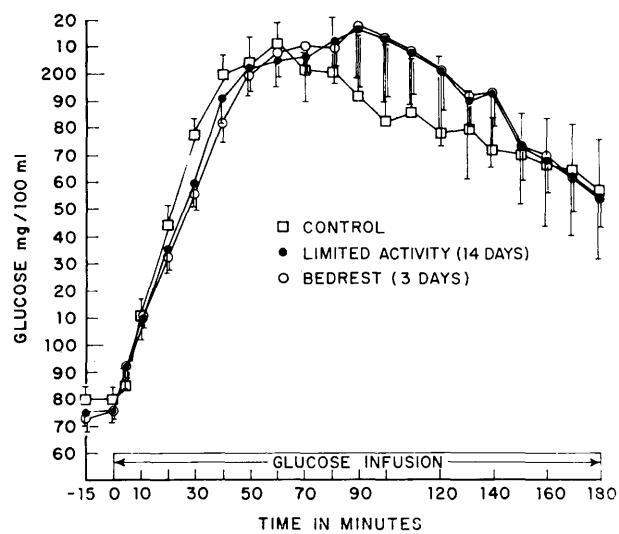

FIG. 1. Mean (± SEM) venous blood glucose curves. Mean venous glucose concentration prior to and at five-minute intervals during the 180-min. glucose infusion were not significantly different among the three groups.

TABLE 1

Glucose loads, arteriovenous (AV) glucose differences, and peripheral glucose uptake during glucose infusion

	Net glucose loads* (gm.) (mean ± SEM)	Urinary glucose (gm.) (mean ± SEM)	AV† glucose difference (mg./100 ml.) (mean ± SEM)	Forearm blood flow (ml./100 ml. muscle/min.) (mean ± SEM)	Peripheral glucose (mg./100 ml. muscle/min.) (mean ± SEM)
Control (C)	183.7 ± 8.3	11.8 ± 2.6	51.2 ± 2.6	3.89 ± 0.11	1.86 ± 0.08
Bedrest (B)	144.2 ± 13.1	8.0 ± 2.5	33.6 ± 2.8	3.83 ± 0.15	1.02 ± 0.19
Limited activity (LA)	155.6 ± 17.8	19.4 ± 4.5	47.3 ± 2.9	4.97 ± 0.17	2.18 ± 0.13
C × B‡	< .05		< .001	> .05	< .05
C × LA	> .05		> .05	< .001	> .05

* Infused glucose loads needed to produce the control venous glucose curve or to reproduce the control glucose curves; the result of subtracting the urinary glucose excreted from the total glucose infused.
† Mean values represent the mean of the individual AV differences from the five- through 180-min. samples.
‡ *T*-test for paired observations.

bedrest and limited activity periods. The seven subjects had a mean weight gain of 1.2 ± 2.2 lb. (SEM) during the bedrest period and during the limited activity period the mean weight gain was 0.5 ± 1.5 lb. above the control.

Venous blood glucose curves. Mean pre-infusion glucose values were unchanged after three days of absolute bedrest and after fourteen days of limited activity from control values. The mean venous blood glucose curves are given in figure 1. There were no significant differences between glucose concentrations calculated at ten-minute intervals during the glucose infusions. Net glucose loads were calculated by subtracting the amount of glucose in the urine from the total glucose administered during each infusion (table 1). The mean net glucose load required to produce the control curves was 183.7 ± 8.3 gm. and 155.6 ± 17.8 gm. during limited activity. These were not significantly different. Following three days of bedrest there was a significant decrease in the mean amount of glucose needed to reproduce the same curves (144.2 ± 13.1 gm.).

Arteriovenous (AV) glucose differences, forearm blood flow and glucose uptake prior to glucose infusion. Mean fasting pre-infusion AV glucose difference was less after three days of bedrest (0.4 ± 1.2 mg./100 ml.) as compared to control (8.8 ± 2.7 mg./100 ml.). Mean fasting AV glucose difference following limited activity (4.8 ± 1.6 mg./100 ml.) was not statistically different from control. The mean forearm blood flow following three days of bedrest (3.1 ± 0.29 ml./100 ml. muscle/min.) was not significantly altered as compared to the control (3.72 ± 0.34 mg./100 ml. muscle/min.). Following limited activity the mean forearm blood flow was increased (5.22 ± 0.47 ml./100 ml. muscle/min.) when compared to control. The calculated mean peripheral glucose uptake was significantly lower after three days of bedrest (0.01 ± 0.003 mg. glucose/100 ml. muscle/min.) as compared to control (0.41 ± 0.16 mg. glucose/100 ml. muscle/min.) but unchanged following limited activity (0.33 ± 0.10 mg. glucose/100 ml. muscle/min.), despite an elevation in forearm blood flow.

Arteriovenous glucose differences, forearm blood flow and peripheral glucose uptake during glucose infusion. Mean values obtained from the five- through 180-min. samples during the glucose infusion are given in table 1. Mean arteriovenous glucose difference was unchanged following limited activity, but significantly depressed following three days of absolute bedrest. Mean peripheral glucose uptake following three days of bedrest was

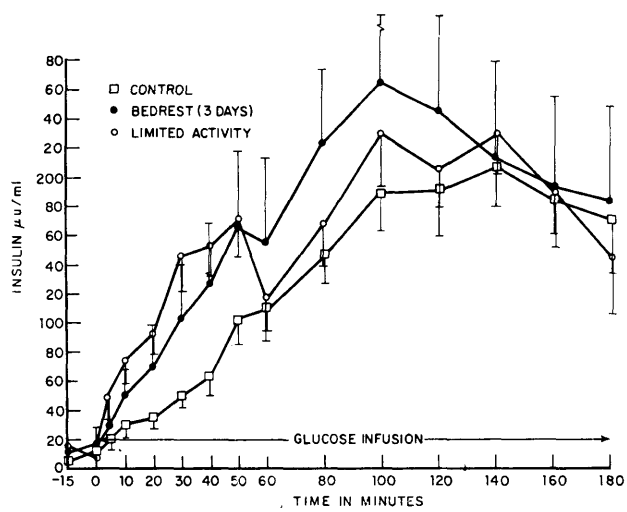

FIG. 2. Mean (± SEM) immunoreactive insulin concentrations before and during glucose infusion.

significantly lower than the control (1.02 ± 0.19 mg. glucose/100 ml. muscle/min. vs. 1.86 ± 0.08 mg. glucose/100 ml. muscle/min.). Following the fourteen days of limited activity, the calculation of forearm glucose uptake resulted in higher mean value as compared to the control value due to an increase in peripheral blood flow.

Serum immunoreactive insulin concentrations prior to and during glucose infusion. Serum immunoreactive insulin values prior to and during the glucose infusion are given in figure 2. Mean fasting, pre-infusion serum insulin values were no different when comparing control (8.4 ± 2.2 μU./ml.), three-day bedrest (7.4 ± 2.8 μU./ml.) and limited activity (7.7 ± 2.5 μU./ml.) values. Mean serum immunoreactive insulin values during the glucose infusion were not significantly different among the groups.

Oral glucose tolerance tests in exercising and nonexercising subjects at bedrest

Subjects that exercised throughout the study had a mean weight gain of 0.5 ± 0.9 lb. during the bedrest period. The subjects that did not exercise during the bedrest period had a mean weight gain of 1.2 ± 0.5 lb. Glucose and immunoreactive insulin values before and after the glucose ingestion are given in table 2 and illustrated in figure 3. There was no significant difference in glucose values when comparing the exercise and nonexercise group during the control and bedrest periods. The subjects that continued to exercise throughout the bedrest period had fasting and sixty-minute postglucose ingestion values similar to their control. Glucose values at 120 and 180 min. following the glucose load in the exercise group, however, were significantly elevated above their control values. Subjects that did not exercise during the bedrest period had fasting, 60, 120 and 180 min. glucose values significantly higher than their control values, despite serum immunoreactive insulin values at sixty and 120 min. postglucose ingestion that were significantly elevated when compared to their control response.

Intravenous insulin tolerance tests during bedrest

As in previous studies the subjects had a slight weight gain during the bedrest period. The mean weight gain was 0.8 ± 0.5 lb. after fourteen days of bedrest. Plasma glucose values before and after insulin administration are illustrated in figure 4. While there were no changes

TABLE 2

Oral glucose tolerance tests during prolonged bedrest: Effect of exercise

		Control					Bedrest				
Subject	Test*	0	60	120	180	Insulin† area	0	60	120	180	Insulin† area
Exercise group											
JF	glucose	86.2	87.6	59.7	76.7		85.7	130.2	90.8	80.4	
	insulin	16.0	24.0	4.0	—	332	13.0	115.0	7.0	13.0	5,967
DS	glucose	62.8	80.0	73.8	60.2		92.5	122.5	113.9	85.7	
	insulin	15.0	34.0	27.0	3.0	1,680	19.0	86.0	67.0	4.0	6,540
RB	glucose	54.1	63.3	60.7	55.1		81.6	—	109.7	80.1	
	insulin	4.0	79.0	8.0	4.0	4,740	6.0	58.0	4.0	—	3,840
JS	glucose	82.1	77.9	74.8	60.7		87.8	82.8	82.1	83.9	
	insulin	23.0	28.0	8.0	4.0	338	16.0	58.0	4.0	—	2,184
glucose	mean	71.3	77.2	67.3	63.2		86.9	111.6	99.1	82.5	
	SEM	7.7	5.1	4.1	4.7		2.3	15.0	7.6	1.4	
insulin	mean	14.5	41.3	11.8	3.7	1,772	13.4	86.3	33.0	10.3	4,633
	SEM	3.9	12.8	5.2	0.3	1,039	2.8	16.5	16.1	3.2	1,002
Nonexercise group											
JB	glucose	65.8	89.4	65.2	65.2		85.7	138.2	94.3	54.0	
	insulin	11.0	63.0	26.0	13.0	3,900	31.0	143.0	39.0	14.0	7,040
SR	glucose	62.5	117.6	93.0	62.3		85.7	167.6	154.8	111.2	
	insulin	15.0	69.0	16.0	11.0	3,276	8.0	157.0	139.0	59.0	13,740
RB	glucose	63.6	76.5	65.8	58.5		87.8	126.1	117.3	78.0	
	insulin	7.0	43.0	19.0	7.0	2,880	4.0	67.0	92.0	7.0	8,880
DK	glucose	75.0	80.1	62.1	62.9		86.0	114.0	101.4	80.7	
	insulin	13.0	66.0	22.0	2.0	3,567	3.0	72.0	—	33.0	5,310
glucose	mean	66.7	90.9	71.5	62.2		86.3	136.5	116.9	81.0	
	SEM	2.8	9.3	7.2	1.4		0.5	11.5	13.5	11.7	
insulin	mean	11.5	60.3	48.3	8.3	3,406	11.5	109.8	90.0	28.3	8,743
	SEM	1.7	5.9	26.0	2.4	217	6.6	23.4	28.9	11.6	1,818

* Glucose (mg./100 ml.); insulin (μU./ml.).

† Area subtended by serum insulin curve and integrated expressed as μU./min./ml.

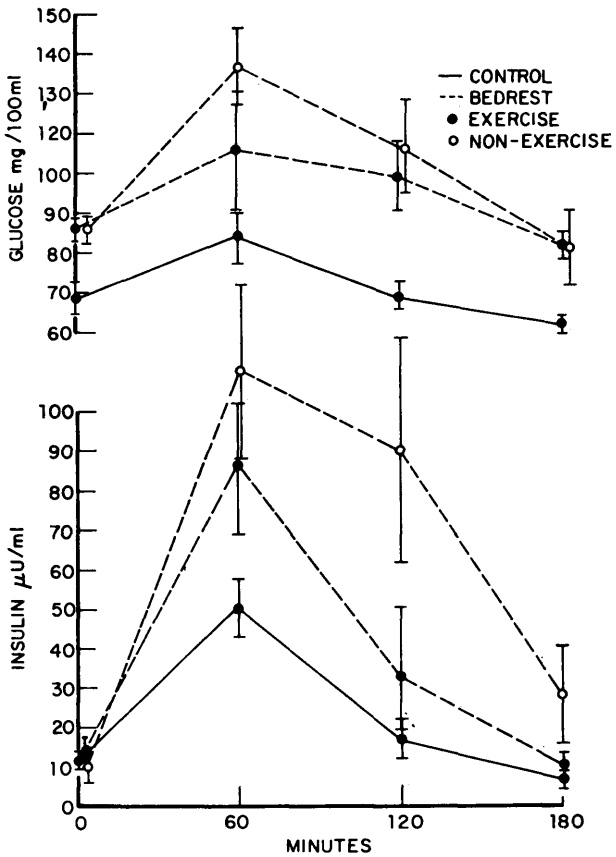

FIG. 3. Mean (± SEM) plasma glucose and serum immunoreactive insulin during glucose tolerance tests in exercising and nonexercising subjects. Glucose and insulin values during the control when all subjects exercised were similar when comparing the two groups. Glucose tolerance tests were done on the fortieth day of the control period and on the thirty-fifth day of the bedrest period.

in fasting glucose concentrations after bedrest, there was a greater fall in mean plasma glucose twenty and thirty minutes after insulin during the control as compared to the bedrest response (41.6 ± 3.4 mg./100 ml. vs. 63.8 ± 5.5 mg./100 ml. and 44.0 ± 3.4 mg./100 ml. vs. 61.9 ± 6.3 mg./100 ml.).

Intravenous glucose tolerance tests in control and immobilized monkeys

Monkeys that were immobilized maintained their weight throughout the period of immobilization. Intravenous glucose tolerance tests in the normal controls and in the immobilized monkeys are given in table 3 and illustrated in figure 5. The mean glucose disappearance rate (K_G) for the immobilized monkeys was significantly less than the normal monkeys, 4.81 ± 0.26 with a range of 3.83 to 6.30.

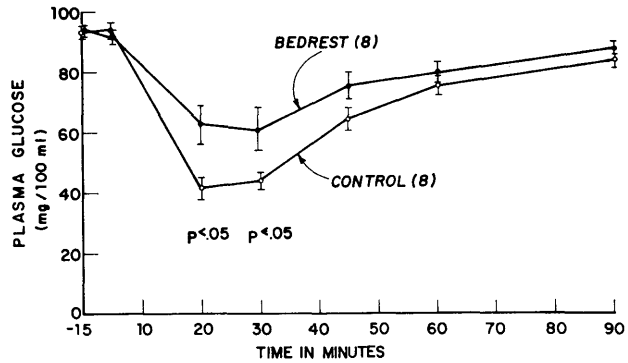

FIG. 4. Plasma glucose following 0.1 U. per kg. of body weight of Regular insulin prior to and on the fourteenth day of absolute bedrest in eight subjects (mean ± SEM). Monkeys immobilized from two to sixteen weeks are grouped together.

DISCUSSION

The significant reduction in peripheral glucose uptake in these studies indicates that glucose intolerance occurs as early as seventy-two hours after the onset of absolute bedrest. The failure of the forearm muscles during bedrest to utilize glucose is secondary to peripheral insulin resistance and not the consequence of insulin deficiency since bedrest insulin concentrations were equal to or slightly greater than the control values. Moreover, subjects at bedrest are resistant to exogenously administered insulin as indicated by a smaller fall in glucose following insulin administered after bedrest as compared to control. Fasting insulin and glucose concentrations, however, were unchanged following three days of bedrest as compared to the significant elevation in glucose and insulin after fourteen days of bedrest in a previous study,[4] and after thirty-five days of bed-

TABLE 3

Glucose disappearance rates (K_G) following intravenous glucose administration in normal and vertically immobilized monkeys

	Immobilized			
Non-immobilized	2 weeks	6 weeks	9 weeks	16 weeks
4.92	3.30	1.86	2.76	2.76
5.77	2.77			
4.95				
6.30				
4.33				
3.83				
5.13				
3.90				
4.30				
4.95				
4.81 (Mean)		2.69*		
0.26 (SEM)		0.23		

* Represents the mean of all of the immobilized animals.

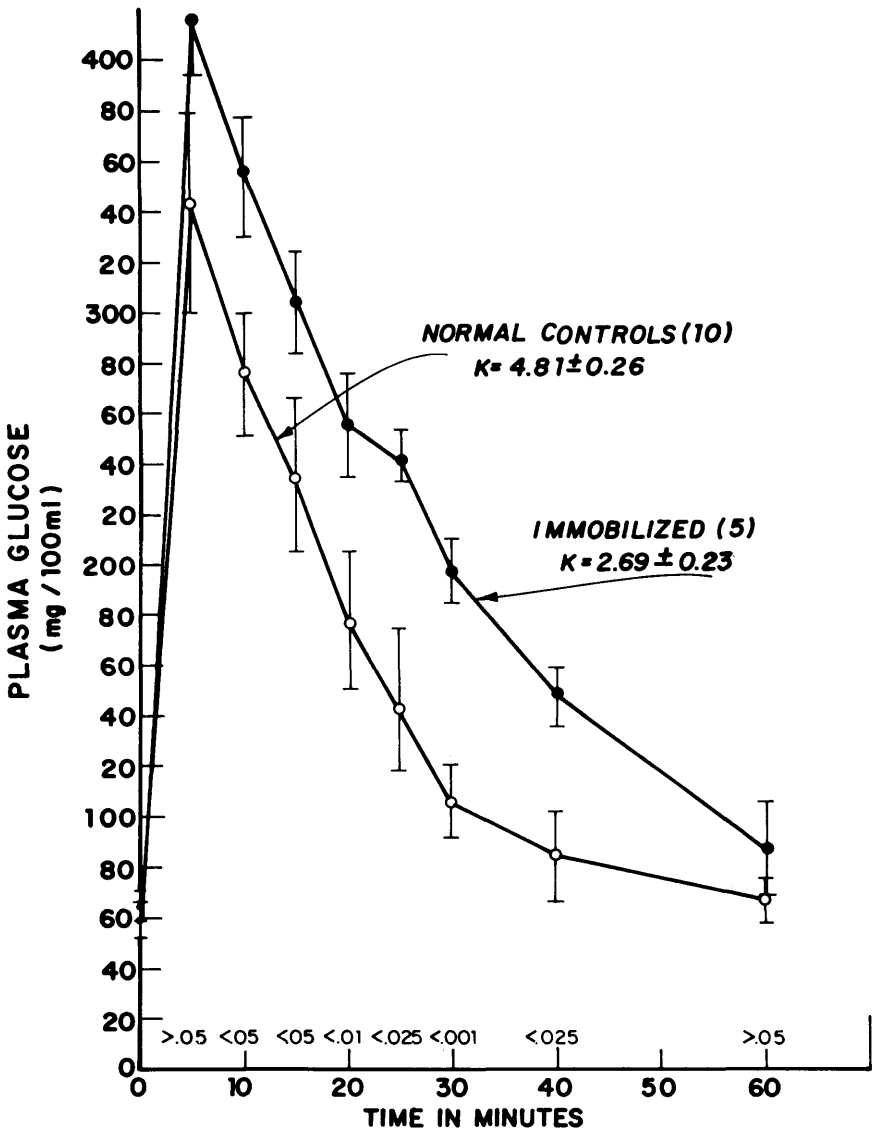

FIGURE 5

Mean (± SEM) plasma glucose concentration following intravenous administration of glucose (1 gm. per kg. body weight) in normal and vertically immobilized monkeys.

rest in the nonexercising group in this study. In addition, peripheral glucose uptake appears to diminish progressively during the course of bedrest from 82 per cent of control at three days to 56 per cent of control after fourteen days of bedrest.[4]

Physical inactivity, however, was accomplished in these and previous studies by the use of absolute bedrest, which by necessity involves maintenance of the horizontal position. Concomitant with the physical deconditioning, therefore, there is a change in the gravitational vector acting on the fluid and semifluid components of the body. These changes have been estimated to be a reduction to approximately one seventh of the force of gravity.[10] The reduction in gravitational forces by bedrest has been shown to cause marked cardiovascular plasma volume and extracellular fluid changes.[10] The relative contribution of the physical deconditioning and the change in gravitational vector to any of the physiologic changes of bedrest, including changes in glucose metabolism, has not been evaluated previously. The forearm glucose uptake studies during limited physical activity were done in order to delineate the effects of minimal erect physical activity on glucose uptake. Forearm glucose uptake, the glucose loads required to produce equal venous glucose curves and arteriovenous glucose differences following fourteen days of limited activity, were unchanged as compared to the control. It would appear from these results that the physical activity

required to stand for three hours per day and/or the assumption of the erect posture alone prevents the bedrest induced deterioration in glucose tolerance. To evaluate these two components, glucose tolerance tests were done in exercising and nonexercising subjects at bedrest. Exercise for one hour per day during bedrest resulted in less deterioration in glucose tolerance than observed in subjects at bedrest who did not exercise. Further evidence that the change in gravitational vector of the subjects plays a minor role in the glucose intolerance of bedrest is evident from the results obtained with vertically immobilized rhesus monkeys. Significant glucose intolerance was noted in the immobilized groups of monkeys as compared to the control. Since there is no change in the gravitational vector in the immobilized animals, the impairment in glucose tolerance appears to be related to the inactivity associated with immobilization.

It has been long recognized that physical activity has an insulin-like effect. Goldstein[11] demonstrated a circulating humoral factor that was released from exercising muscle. This factor had a significant hypoglycemic effect in resting parabiotic animals. Whether physical deconditioning results in an alteration in this humoral factor is unclear.

It would appear that decreased physical activity whether produced by absolute bedrest even for short periods of time or by immobilization, results in significant peripheral insulin resistance and glucose intolerance. There is little evidence from previous studies[2,4] to indicate that alterations in such insulin antagonists as growth hormone, free fatty acids or corticosteroids play a significant role in these changes in glucose utilization. Since the defect in glucose utilization can appear after only three days of bedrest the role of physical inactivity should be considered in the interpretation of glucose tolerance tests, especially in the bedridden hospitalized patient.

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