Glucose Intolerance in Man During Prolonged Exposure to a Hypobaric-hyperoxic Environment

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SUMMARY

Eight subjects were exposed to a hypobaric (258 mm. Hg)-hyperoxic (100 per cent oxygen) environment for thirty days. Standard oral glucose tests were done during a control period of normal pressure and atmosphere, twenty-four hours after completing the thirty-day exposure and during a fifteen-day recovery. Exercise was uniform during the control period; however, during exposure and recovery periods four subjects continued daily exercise and the other four were maintained on limited activity (bedrest with bathroom privileges). Diet was constant throughout, containing 350 gm. of carbohydrates. Mean exposure period fasting (104.5 ± 6.5 mg./100 ml. S.E.M.) and sixty-minute (145 ± 18.5 mg./100. ml.) glucose values were significantly greater than corresponding control period fasting (87.1 ± 1.6 mg./100 ml.) and sixty-minute (105 ± 4.6 mg./100 ml.) control values. Mean plasma glucose values at 120 and 180 minutes during exposure to the test atmosphere were greater, but not significantly different than during control periods. Results of the glucose tolerance tests done fifteen days post-exposure showed mean fasting 60-, 120- and 180-minute values to be significantly higher than the pre-exposure controls but similar to the exposure values. Serum immunoreactive insulin concentrations immediately after exposure and during recovery were unchanged from control levels. No difference in either glucose or insulin values could be detected between the exercise and nonexercise groups. It is suggested that prolonged exposure to hypobaric-hyperoxic environments adversely influences glucose tolerance. DIABETES *20*:282-85, May, 1971.

There is concern that the unique stresses of space flight may be conducive to abnormal glucose metabolism. This conjecture is based upon the fragmentary evidence of pre- and postflight blood glucose levels, since, to date, no inflight measurements have been made. Analyses of available United States and Russian reports, which include blood glucose studies, have revealed uniform increases in postflight glucose concentrations as compared to preflight values.[1,2]

It is difficult to determine if the changes in glucose concentration are due to weightlessness or to some of the other aspects of space flight such as alterations in barometric pressure and gas composition, altered patterns of physical activity, as well as accelerative and vibratory forces. Recently we demonstrated significant glucose intolerance following simulated weightlessness using absolute bedrest as a model.[3] Significant alterations in such glucoregulatory hormones as cortisol and growth hormone have been found following acute and chronic acceleration in man.[4] The present study was designed to explore the influence of the altered barometric pressure and gas composition of the space vehicle (i.e., the hypobaric-hyperoxic environment) upon glucose and insulin in man.

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METHODS AND MATERIALS

Eight normal males between the ages of 18 and 21 were studied. All were volunteers who consented to the study after being informed of its potential hazards and complications. Each subject had a negative family his-

tory for diabetes mellitus, a normal oral glucose tolerance test, and was within 10 per cent of his ideal weight. The experiment consisted of a control period of two weeks immediately prior to the thirty-day exposure to an ambient pressure of 258 mm. Hg and an alveolar P_{O_2} (P_AO_2) of approximately 170 mm. Hg ($P_{N_2} \cong$ 1 mm. Hg) with a constant temperature of 24° C and relative humidity of 50 per cent, followed by a fifteen-day recovery period. The entire study was conducted within the confines of a 3,000 cubic feet environmental chamber. The control and recovery periods were conducted at normal conditions of 746 mm. Hg (P_AO_2 of 98.5 mm. Hg) with temperature and humidity maintained at exposure levels. Throughout the study the subjects were fed a reconstituted freeze-dehydrated diet consisting of 2,700 kilocalories and containing 350 gm. of carbohydrates per day.

All subjects exercised daily on a bicycle ergometer during the control period for two 20-minute periods at a constant heart rate of 160 beats per minute. During the exposure and recovery periods the subjects were divided into active and inactive groups of four each. The active group continued the same daily exercise while the inactive group was limited to bedrest with bathroom privileges and freedom of movement in bed. Oral fasting glucose tolerance tests (100 gm. of glucose*) were performed on the 14th day of the control period, twenty-four hours after the thirty-day exposure and on either the 10th, 11th, 14th or 15th days during the recovery period.

Serum glucose concentrations were determined by the potassium ferricyanide-ferrocyanide method on a Technicon AutoAnalyzer.[5] Serum immunoreactive insulin (IRI) was done in duplicate according to a modification of the technic of Morgan and Lazarow.[6] Each subject's response twenty-four hours after the exposure and during the recovery period was compared to his response during the control period. Significance was tested by the Student's "t"-test for paired observations and probability levels of 5 per cent or less were accepted as significant.

RESULTS

The mean (± S.E.M.†) glucose values prior to and following oral glucose ingestion are illustrated in figure 1. The mean fasting glucose value twenty-four hours postexposure (104.5 ± 6.5 mg./100 ml.*) was significantly greater than the mean during the control period

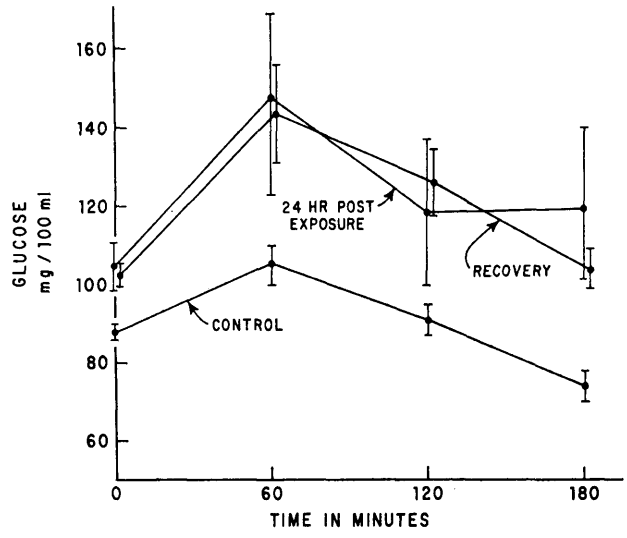

FIG. 1. Mean (± S.E.M.) glucose values prior to and following oral glucose ingestion in eight normal subjects.

(87.6 ± 1.6 mg./100 ml.). Also, sixty minutes following the oral glucose loads, the mean glucose concentration was significantly greater twenty-four hours postexposure than the equivalent control value. However, twenty-four hours postexposure values at 120 and 180 minutes were higher, but not significantly different from control values. Surprisingly, glucose tolerance tests during the recovery period revealed serum glucose concentrations that were also significantly greater than the control value at all points, but not different from the twenty-four-hour postexposure values, indicating that there was no improvement in glucose tolerance during the fifteen-day recovery phase.

The mean integrated areas subtended by the immunoreactive insulin (IRI) curves are shown in figure 2. There were no statistically significant differences in

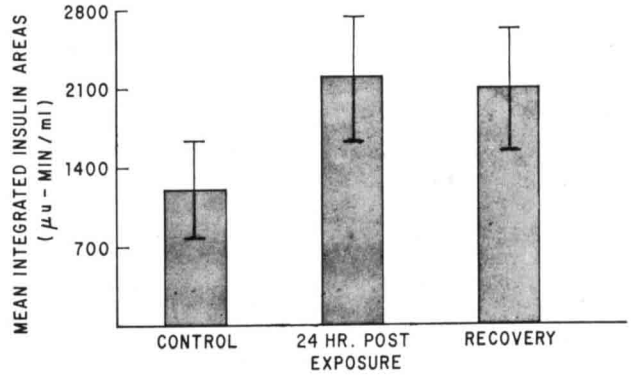

FIG. 2. Mean (± S.E.M.) integrated serum immunoreactive insulin areas in eight normal subjects following 100 gm. of oral glucose.

* Dextrose, USP, Hydrous (Lot. 3922), Corn Products Company, New York, N. Y.

† Standard error of the mean.

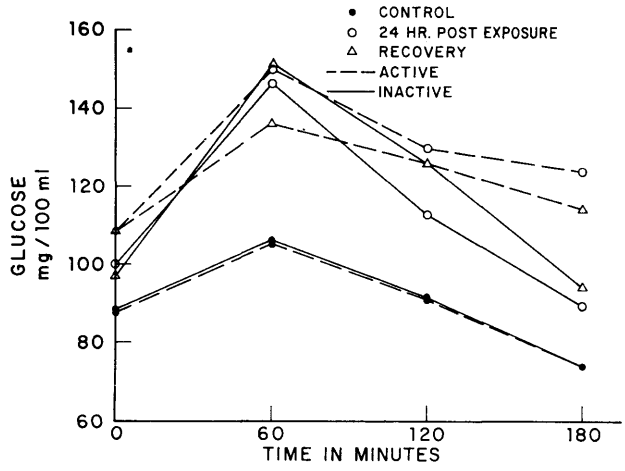

FIG. 3. Serum glucose (Mean) prior to and following oral glucose ingestion in active (— — — —) and inactive (————) subjects.

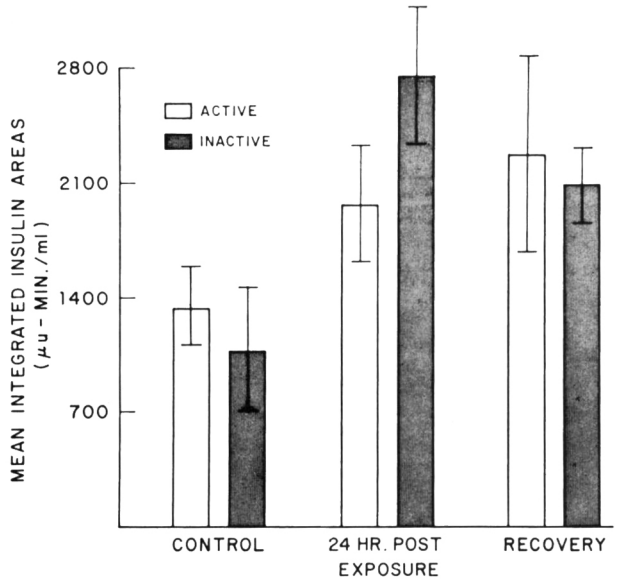

FIG. 4. Integrated serum immunoreactive insulin areas (Mean ± S.E.M.) in active and inactive subjects.

mean areas when comparing the control to the post-exposure and recovery values. Mean fasting and post glucose ingestion IRI concentrations obtained twenty-four hours postexposure and during the recovery period were elevated, but not significantly different from control levels.

The serum glucose concentrations and mean integrated insulin areas for the glucose tolerance tests, comparing the subjects that exercised to those that remained inactive are shown in figures 3 and 4. There were no significant differences either in serum glucose concentrations or integrated insulin areas, when comparing the active to the inactive group during any of the three periods.

DISCUSSION

Past studies evaluating glucose metabolism in animals and man exposed to various oxygen environments are summarized in figure 5. They are classified according to variations in altitude, P_{O_2} and duration of exposure. Acute exposure of dogs to a hypobaric (258 mm. Hg)—normoxic (152 mm. Hg P_{O_2}) environment has produced significant increases in glucose disappearance rates.[7-9] Other studies on dogs and man exposed acutely to varied hypobaric-hypoxic conditions have shown fasting hyperglycemia and glucose intolerance,[10-13] however. The authors postulated this is due to the stress of hypoxia and the subsequent release of epinephrine and cortisol. Epinephrine has been shown to inhibit insulin release in the hypoxic dog[14] and cortisol has a well documented diabetogenic effect.[11] On the other hand, chronic exposure to the hypobaric-hypoxia resulted in an increase in glucose tolerance.[15,16] Data from experiments in rats exposed to isobaric (760 mm. Hg)-hyperoxic (P_{O_2} 760 mm. Hg) environments demonstrated that glycolytic enzymes were inhibited by the high oxygen tension and resulted in significant hyperglycemia.[17-19] When comparing these different environments, normal or increased glucose tolerance is found either in the presence of normoxia or chronic hypoxia, while acute hyperoxia has been shown to cause hyperglycemia and impaired glucose tolerance.

This study has shown that chronic exposure to hypobaric-hyperoxia also results in fasting hyperglycemia and glucose intolerance which persists as long as fifteen days following the exposure. The mechanism of this resulting hyperglycemia cannot be defined by this ex-

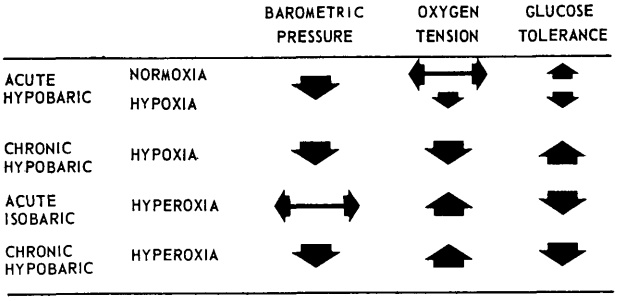

FIG. 5. Summary of past studies evaluating glucose tolerance in animals and man exposed to various oxygen tension and barometric pressures. An arrow pointing upward indicates an increase in glucose tolerance and an arrow pointing downward indicates deterioration in glucose tolerance. The arrows pointing horizontally indicate no change in glucose tolerance.

periment alone. As suggested by Horn et al.,[17] Haugaard[20] and Dickens,[19] oxygen at high partial pressures poisons not only the glycolytic pathway by oxidizing the sulfhydryl groups on glyceraldehyde 3-phosphate dehydrogenase, but the tricarboxcyclic acid cycle, because oxidation of sulfhydryl groups inactivates AcetylCoA. Although these latter authors' studies were done at a P_{O_2} of 760 mm. Hg, one might expect the same effect during a more prolonged exposure of thirty days at an alveolar P_{O_2} of 170 mm. Hg, but perhaps to a lesser degree and with a slower rate of onset. It would appear, moreover, that the changes in glucose tolerance observed in this study were secondary to the increased oxygen tensions *rather than due to changes in barometric pressure.*

The possibilities that diet or confinement might have influenced glucose tolerance was considered but seemed unlikely since subjects have been exposed to other environmental parameters in the same chamber for much longer periods of time while on similar diets without abnormal glucose tolerance. A parallel study with the identical experimental design except for the altered ambient pressure and oxygen tension would have been ideal, but was not feasible because of time and space limitations.

In an attempt to simulate the space capsule environment, one half of the subjects in this study were kept on limited physical activity. Glucose tolerance was not altered by the limited activity beyond that found as a result of the hypobaric-hyperoxic environment. This is in agreement with previous studies in this laboratory which demonstrate even minor degrees of physical activity prevent the bedrest induced deterioration in glucose tolerance.[21]

In summary, exposure of normal young subjects to a prolonged simulated space environment of 100 per cent O_2 (P_AO_2 170 mm. Hg) and a 258 mm. Hg barometric pressure results in significant glucose intolerance. It is suggested that if the exposure time to such high oxygen tensions as used in this study were to be increased, as might occur in interplanetary travel, significant alterations in glucose metabolism will result.

ACKNOWLEDGMENT

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