Glucose turnover in response to exercise during high- and low-FI\textsubscript{O}\textsubscript{2} breathing in man

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COOPER, DAN M., DAVID H. WASSERMAN, MLADEN VRANIC, AND KARLMAN WASSERMAN. Glucose turnover in response to exercise during high- and low-FI\textsubscript{O}\textsubscript{2}, breathing in humans. Am. J. Physiol. 251 (Endocrinol. Metab. 14): E209-E214, 1986.—The purpose of this study was to assess whether breathing high or low concentrations of O\textsubscript{2} could affect glucose turnover during exercise in man. Ten healthy subjects performed two constant work-rate exercise tests, one when the fraction of inspired O\textsubscript{2} (FI\textsubscript{O}\textsubscript{2}) was 0.15 and the other at the same work rate but when the FI\textsubscript{O}\textsubscript{2} was 0.80. The work rate for each subject was chosen so that blood lactate would be elevated during hypoxia, but would be lower during hyperoxia. Glucose appearance (R\textsubscript{A}) and disappearance (R\textsubscript{D}) were measured using the primed, constant infusion of [3-\textsuperscript{3}H]glucose. Although the work rate was the same during hypoxia and hyperoxia in each subject, hypoxic exercise was accompanied by a significantly larger rest to exercise increase in R\textsubscript{A} (\Delta R\textsubscript{A}) compared with hyperoxia by 265%. Similarly, \Delta R\textsubscript{D} was greater during hypoxia than during hyperoxia by 188%. Lactate to pyruvate ratios were significantly higher during hypoxic exercise suggesting a shift in the cell redox to a more reduced state. Insulin and glucagon were not affected by the FI\textsubscript{O}\textsubscript{2}, but both epinephrine and norepinephrine were increased during hypoxic exercise, which may explain the increase in R\textsubscript{D}. The regulation of blood glucose during exercise in vivo appears to be dependent on the availability of oxygen to the working muscle cells.

IN MAMMALIAN MUSCLE TISSUE, the level of contractile activity and the PO\textsubscript{2} of the blood perfusing the cells are known to be determinants of glucose uptake (2, 10, 17, 19, 24). It has also been demonstrated that both intense exercise and low PO\textsubscript{2} are accompanied by increased blood lactate concentration and changes in the cellular redox potential to a more reduced state (2, 10). These observations have led to the hypothesis that hypoxia and contractile activity stimulate muscle cell glucose uptake by a single mechanism related to the energy state of the muscle cells (26).

When normal subjects exercise at a constant load, lactate accumulates in the blood only if the work rate is above a certain level (14, 30). Breathing a low fraction of inspired O\textsubscript{2} (FI\textsubscript{O}\textsubscript{2}) reduces the work rate threshold for blood lactate accumulation (12, 13). Conversely, the threshold for lactate increase occurs at a higher work rate when the FI\textsubscript{O}\textsubscript{2} is high. This suggests that O\textsubscript{2} availability can interact with work rate to affect glucose turnover.

The combined effect of hypoxia and contractile activity in exercising man is not known, i.e., the extent to which changing O\textsubscript{2} availability to working muscle will affect muscle glucose uptake or hepatic production. The purpose of this investigation was to examine glucose kinetics (uptake and production) and regulation in exercising subjects breathing high and low concentrations of inspired O\textsubscript{2}, thereby changing the PO\textsubscript{2} of the blood perfusing the muscle cells, but without altering the work rate. Thus glucose turnover was measured at a single work rate under conditions of high and low FI\textsubscript{O}\textsubscript{2}. In each subject this work rate was chosen so that lactate concentrations were elevated during exercise when the FI\textsubscript{O}\textsubscript{2} was low, but lactate concentrations were lower when the FI\textsubscript{O}\textsubscript{2} was high.

**METHODS**

**Population**

Ten male volunteers ranging in age from 19 to 37 yr in good health and without any prior history of chronic respiratory or other disease, comprised the study population. The group was heterogeneous in terms of fitness as judged by the VO\textsubscript{2max} normalized to body weight, but none were in training as athletes at the time of the study. The subjects' age, weight, VO\textsubscript{2max}/kg body weight, and specifically selected work rate used in the studies are shown in Table 1. Informed consent was obtained.

**Protocol**

The exercise protocol consisted of three separate cycle ergometry sessions on 3 different days for each subject. On day 1, three progressive exercise tests were performed ["ramp" type protocol (32)] for the noninvasive determination of the lactate or anaerobic threshold under conditions of room air, FI\textsubscript{O}\textsubscript{2} of 0.15 and FI\textsubscript{O}\textsubscript{2} of 0.80 chosen randomly. Each of these studies lasted ~15 min. There was a 40-min rest period between each test. Based on these studies, a single work rate was chosen for subsequent constant work rate exercise protocols to be per-
formed on days 2 and 3. This work rate was above the subject's lactate threshold under conditions of low FIO2 but below it under conditions of high FIO2.

Glucose turnover during the selected constant work rate exercise (Table 1) was measured on days 2 and 3 (separated by a 2 wk interval). Since the measurements of glucose uptake and production requires relatively long periods of exercise, only moderate hypoxia (FIO2 of 0.15) could be utilized. To maximize the difference in O2 availability to the working muscle, it was decided to compare the hypoxic protocol with exercise done at an FIO2 of 0.80. The order of the high- and low-FIO2 protocols was selected randomly.

The constant work rate protocols were performed in the morning after an overnight fast. There was a 120-min tracer equilibration period before exercise to allow for a steady-state concentration of tritiated glucose. Twenty-five minutes before exercise, the subject began breathing the high- or low-O2 mixture. Blood sampling was performed every 5 min starting 20 min before exercise and continued throughout the 40 min of the exercise period.

**Measurement of Gas Exchange Parameters**

The subjects breathed through a low-impedance turbine volume transducer for measurement of inspiratory and expiratory volumes. Dead space of the mouthpiece and turbine device was 170 ml. Respiratory PO2 and PCO2 were determined by mass spectrometry from a sample drawn continuously from the mouthpiece at 1 ml/s and were displayed digitally. We could therefore verify that no leakage of room air gas occurred during the high- and low-O2 studies. The electrical signals from these devices underwent analogue to digital conversion for the on-line breath-to-breath computation of O2 uptake (VO2, STPD), CO2 output (VCO2, STPD), and expired ventilation (VE, BTPS) as previously described (1). Heart rate was measured beat by beat using a modified standard lead I EKG for which three leads were placed on the chest. Saturation of hemoglobin with O2 was measured noninvasively by ear oximetry.

The VO2 max was the highest VO2 achieved by the subject. Determination of the lactate threshold from gas exchange measurements is well described (30, 32). It is based on the coupling of CO2 production and ventilation. When lactate concentration increases during exercise, the excess hydrogen ion is buffered by bicarbonate and CO2 is liberated. The increased CO2 production stimulates ventilation but not O2 uptake. Thus the threshold is measured by finding hyperventilation relative to VO2, i.e., the VO2 above which VE/VO2 and end-tidal PCO2 increase without an increase in VE/VCO2 or a decrease in end-tidal PCO2. Moreover, in constant work rate protocols done above the threshold, VO2 continues to increase between the 3rd and 6th min of exercise (30). This allowed an additional means to verify which subjects were above the threshold during the constant work rate protocol.

**Tracer Methods**

Primed, constant-infusion of [3-3H]glucose was used to measure glucose production (Ra), uptake (Ru), and metabolic clearance rate (MCR = Ra/[glucose]) (15). [3-3H]glucose, 5 μCi/ml, was infused at a constant rate (0.086 ml/min) via an indwelling catheter in the antecubital vein. A priming dose, equivalent to the amount infused in 140 min, was given at the beginning of each experiment before the constant rate infusion. Ra and Ru were calculated using a "modified" single compartment for glucose as described by Steele et al. (22) for the non-steady state. These calculations have been validated for the non-steady-state condition (16).

Another indwelling venous catheter was placed in the antecubital vein of the opposite arm. Both arms rested on platforms, thus, no gripping of handle bars occurred during the studies. Blood samples for the measurement of glucose and tracer were obtained every 5 min throughout the 20 min before exercise and the 40-min exercise session (5 base line, 8 exercise). Plasma for tracer glucose determination was deproteinized using BaOH and ZnSO4, evaporated, and redissolved in distilled water. Samples were counted for 100 min by liquid scintillation spectrometry. Plasma glucose concentration was determined by the glucose oxidase method.

Two base-line and five exercise measurements were made of lactate, pyruvate, immunoreactive insulin (IRI), glucagon (IRG), norepinephrine, and epinephrine. Lactate and pyruvate were measured by the method of Holmhorst (9). Radioimmunoassays were used to measure IRI (8) and IRG (5). Catecholamines were measured by the enzymatic radioimmunoassay technique (18).

**Data Analysis**

The test statistics consisted of the means, for each subject, of the base-line (preexercise) and exercise measurements of the variables listed above. Analysis of variance (repeated measurements) was used to test the effect of the high and low FIO2 on the base-line values, and when ANOVA was significant, mean values were compared using a modified t test (27). To compare the effects of hypoxic exercise with hypoxic exercise on glucose turnover and counterregulation, base-line to exercise differences in each variable (designated, for example, as ΔR4) were analyzed using paired t tests. Standard techniques of linear regression were used to assess changes in VO2 and O2 saturation over the period of the exercise.

**TABLE 1. Age, weight, VO2 max, and work rate studied**

| Subject No. | Age, yr | Weight, kg | VO2 max, ml O2, min⁻¹ kg⁻¹ | Work Rate, W | Work Rate, % max PO2 0.21 |
|-------------|---------|------------|-----------------------------|--------------|---------------------------|
| 1           | 35      | 68.5       | 49.6                        | 140          | 50                        |
| 2           | 19      | 71.0       | 36.7                        | 90           | 47                        |
| 3           | 37      | 72.7       | 48.3                        | 160          | 45                        |
| 4           | 20      | 60.0       | 30.0                        | 50           | 33                        |
| 5           | 25      | 71.5       | 46.2                        | 100          | 40                        |
| 6           | 27      | 82.2       | 40.0                        | 120          | 38                        |
| 7           | 30      | 84.6       | 50.3                        | 120          | 40                        |
| 8           | 21      | 69.1       | 33.3                        | 95           | 48                        |
| 9           | 19      | 71.4       | 36.4                        | 65           | 40                        |
| 10          | 19      | 75.5       | 62.9                        | 110          | 33                        |
GLUCOSE TURNOVER DURING EXERCISE IN HIGH AND LOW \( F_iO_2 \)

study. Statistical significance was taken at the \( P < 0.05 \) level. Unless otherwise stated, values are represented as means \( \pm SD \).

RESULTS

Effect of \( F_iO_2 \) on Lactate Threshold

In all 10 subjects, the lactate threshold occurred at a lower work rate and \( V_o2 \) when the \( F_iO_2 \) was 0.15 compared with 0.21 (mean decrease in \( V_o2 \) at the lactate threshold, 19%; Fig. 1). An additional increase was observed at \( F_iO_2 \) of 0.80 compared with the 0.21 studies in 9 of the 10 subjects (mean increase, 15%).

Constant Work Rate Protocols

Gas exchange. \( V_o2 \) increased significantly with the duration of exercise between the 3rd and 6th min of hypoxic exercise (mean correlation coefficient \( r \) of 0.52) confirming, by gas exchange criteria, that the exercise done during hypoxia was above the threshold. The mean \( O_2 \) saturation during hypoxic exercise was 91 \( \pm \) 1%. By contrast, during hypoxic exercise, \( O_2 \) saturation did not change and remained between 98 and 100% in all subjects.

Glucose kinetics. Base-line glucose concentration during hypoxia (mean, 96.4 \( \pm \) 8.1 mg/dl) did not differ from that measured during hyperoxia (92.4 \( \pm \) 7.9 mg/dl). Glucose concentrations did not change appreciably during hypoxic or hyperoxic exercise. Glucose concentration during hypoxic exercise was 97.6 \( \pm \) 5.1 mg/dl compared with hyperoxia, 97.4 \( \pm \) 8.6 mg/dl.

Under hypoxic conditions, mean base-line values of \( R_d \) increased from 3.16 \( \pm \) 1.39 mg \( \cdot \) min \( ^{-1} \) \( \cdot \) kg \(^{-1} \) to a mean of 5.43 \( \pm \) 2.13 mg \( \cdot \) min \( ^{-1} \) \( \cdot \) kg \(^{-1} \) during exercise. In contrast, under hyperoxic conditions, mean base-line values of \( R_d \) increased from 3.52 \( \pm \) 1.15 mg \( \cdot \) min \( ^{-1} \) \( \cdot \) kg \(^{-1} \) to a mean of 4.77 \( \pm \) 1.73 mg \( \cdot \) min \( ^{-1} \) \( \cdot \) kg \(^{-1} \) during exercise. The increase in glucose uptake during hypoxic exercise was greater than during hyperoxic exercise in 8 of the 10 subjects. The average \( \Delta R_d \) during hypoxia was greater than during hyperoxia by 265%, \( P < 0.05 \) (Fig. 2). In addition, \( \Delta MCR \) was significantly greater during hypoxic exercise (Fig. 2). The mean resting MCR during hypoxia was 2.94 \( \pm \) 1.17 ml \( \cdot \) min \(^{-1} \) \( \cdot \) kg \(^{-1} \) and increased to 5.66 \( \pm \) 2.23 ml \( \cdot \) min \(^{-1} \) \( \cdot \) kg \(^{-1} \) during hypoxic exercise. The mean resting MCR during hyperoxia was 4.13 \( \pm \) 1.17 ml \( \cdot \) min \(^{-1} \) \( \cdot \) kg \(^{-1} \) and was 4.84 \( \pm \) 1.63 ml \( \cdot \) min \(^{-1} \) \( \cdot \) kg \(^{-1} \) during hyperoxic exercise.

Mean base-line \( R_a \) was higher during hyperoxia compared with hypoxia by 23% (3.90 \( \pm \) 0.95 compared with 3.00 \( \pm \) 1.28 mg \( \cdot \) min \( ^{-1} \) \( \cdot \) kg \(^{-1} \)), but this difference was not statistically significant. \( \Delta R_a \) during hypoxic exercise was greater than during hyperoxic exercise in 9 of the 10 subjects. The average \( \Delta R_a \) during hypoxia was significantly greater than during hypoxia by 188% (Fig. 2). The mean exercise \( R_a \) was 5.56 \( \pm \) 2.13 mg \( \cdot \) min \( ^{-1} \) \( \cdot \) kg \(^{-1} \) during hypoxia and 5.27 \( \pm \) 1.63 mg \( \cdot \) min \( ^{-1} \) \( \cdot \) kg \(^{-1} \) during hyperoxia.

Lactate, pyruvate, and lactate-to-pyruvate ratios. There were no differences in the mean base-line lactate, pyruvate, or lactate-to-pyruvate ratios between the hypoxic and hyperoxic studies (Fig. 3). As expected the increases in lactate (\( \Delta Lactate \)) and pyruvate (\( \Delta Pyruvate \)) were significantly higher during hypoxic exercise. In addition,
the increase in the ratio of lactate to pyruvate during exercise was significantly higher during hypoxia.

**Insulin and glucagon.** Mean IRI was lower during exercise than during the base-line period in both hypoxia and hyperoxia, but these differences were not significant (Fig. 4). There were no significant differences between base-line glucagon in the hypoxic and hyperoxic studies. Similarly, during exercise the hypoxic values did not differ from the hyperoxic values.

Epinephrine and norepinephrine. There were no significant differences between base-line epinephrine in the hypoxic and hyperoxic studies (Fig. 5). However, the increase in epinephrine during hypoxic exercise was significantly greater than during hyperoxic exercise. Similarly, base-line values for norepinephrine did not differ between hypoxia and hyperoxia, but the norepinephrine increase over base line during hypoxic conditions was significantly greater than during hyperoxic conditions.

**DISCUSSION**

The results of this study demonstrate that exercise-induced increases in glucose uptake and production in

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**Fig. 4.** Mean base-line and exercise values of insulin (IRI) and glucagon (IRG) during hypoxia and hyperoxia. Clear bars represent mean ± SE of base-line conditions. Hatched bars represent mean ± SE of the exercise conditions. Concentration of these substances were not significantly affected by exercise or by \( F_{O_2} \).

![Image](https://example.com/figure5.png)

**Fig. 5.** Norepinephrine and epinephrine in response to exercise during hypoxia and hyperoxia. Clear bars represent mean ± SE of base-line conditions. Hatched bars represent mean ± SE of the exercise-induced increase in catecholamines (anorepinephrine, epinephrine). Increase in both substances was significantly greater during hypoxic compared to hyperoxic conditions as indicated by asterisk.
catecholamines have been shown to inhibit glucose uptake by muscle tissue (25), in the present study, glucose uptake was elevated during hypoxic exercise at the same time that catecholamines were increased. The stimulus for glucose uptake in hypoxic exercise appears to be strong enough to mitigate possible inhibition by catecholamines.

Hepatic glucose production was also elevated during hypoxic compared with hyperoxic exercise (Fig. 2). While glucagon has been shown to be an important regulator of glucose production during exercise (6, 11, 23, 28), the levels of IRG during exercise in the present study were unchanged by the FIO2. Catecholamines have been shown to stimulate Rgl in even the absence of changes in the pancreatic hormones (3, 7); thus, the exaggerated catecholamine response observed in hypoxic exercise may have been responsible for the generally greater rate of hepatic glucose production observed during hypoxic exercise. Alternatively, hypoxia may have a direct effect on hepatic glucose production.

The results of this investigation emphasize the robust nature of the homeostatic mechanisms for glucose regulation. The stimulus of hypoxia significantly increased glucose uptake during moderate exercise, but also resulted in an increased glucose production so that blood glucose concentration was maintained within a narrow, presumably "optimal" range. In diseases of the heart, lungs, and blood vessels, reduced tissue O2 availability is commonly encountered with increased lactate concentration. The finding of a normal blood glucose in these conditions may conceal significant alterations in substrate utilization.

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