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Glucose turnover in response to exercise during high- and low- FI_{O_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_{O_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_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_2 (FI_{O_2}) was 0.15 and the other at the same work rate but when the FI_{O_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_a) and disappearance (R_d) were measured using the primed, constant infusion of [$3\text{-}^3\text{H}$]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_d (ΔR_d) compared with hyperoxia by 265%. Similarly, ΔR_a 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_{O_2} , but both epinephrine and norepinephrine were increased during hypoxic exercise, which may explain the increase in R_a . The regulation of blood glucose during exercise in vivo appears to be dependent on the availability of oxygen to the working muscle cells.

hypoxia; hyperoxia; exercise catecholamines; blood glucose regulation; lactate threshold

IN MAMMALIAN MUSCLE TISSUE, the level of contractile activity and the PO_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_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_2 (FI_{O_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_{O_2} is high. This suggests that O_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_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_2 , thereby changing the PO_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_{O_2} . In each subject this work rate was chosen so that lactate concentrations were elevated during exercise when the FI_{O_2} was low, but lactate concentrations were lower when the FI_{O_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 $\dot{V}\text{O}_{2\text{max}}$ normalized to body weight, but none were in training as athletes at the time of the study. The subjects' age, weight, $\dot{V}\text{O}_{2\text{max}}$ /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_{O_2} of 0.15 and FI_{O_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-

TABLE 1. Age, weight, $\dot{V}\text{O}_{2\text{ max}}$, and work rate studied

Subject No.	Age, yr	Weight, kg	$\dot{V}\text{O}_{2\text{ max}}$ /kg, ml $\text{O}_2 \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$	Work Rate, W	Work Rate, % max FI_{O_2} 0.21
1	35	68.5	49.6	140	50
2	19	71.0	36.7	90	47
3	37	72.7	48.1	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

formed on days 2 and 3. This work rate was above the subject's lactate threshold under conditions of low FI_{O_2} but below it under conditions of high FI_{O_2} .

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 (FI_{O_2} of 0.15) could be utilized. To maximize the difference in O_2 availability to the working muscle, it was decided to compare the hypoxic protocol with exercise done at an FI_{O_2} of 0.80. The order of the high- and low- FI_{O_2} 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- O_2 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. Respired PO_2 and PCO_2 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- FI_{O_2} studies. The electrical signals from these devices underwent analogue to digital conversion for the on-line breath-to-breath computation of O_2 uptake ($\dot{V}\text{O}_2$, STPD), CO_2 output ($\dot{V}\text{CO}_2$, STPD), and expired ventilation ($\dot{V}\text{E}$, 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 O_2 was measured noninvasively by ear oximetry.

The $\dot{V}\text{O}_{2\text{ max}}$ was the highest $\dot{V}\text{O}_2$ 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 CO_2 production and ventilation. When lactate concentration increases during exercise,

the excess hydrogen ion is buffered by bicarbonate and CO_2 is liberated. The increased CO_2 production stimulates ventilation but not O_2 uptake. Thus the threshold is measured by finding hyperventilation relative to $\dot{V}\text{O}_2$, i.e., the $\dot{V}\text{O}_2$ above which $\dot{V}\text{E}/\dot{V}\text{O}_2$ and end-tidal PO_2 increase without an increase in $\dot{V}\text{E}/\dot{V}\text{CO}_2$ or a decrease in end-tidal PCO_2 . Moreover, in constant work rate protocols done above the threshold, $\dot{V}\text{O}_2$ 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 $[3\text{-}^3\text{H}]\text{glucose}$ was used to measure glucose production (R_a), uptake (R_d), and metabolic clearance rate ($\text{MCR} = R_d/[\text{glucose}]$) (15). $[3\text{-}^3\text{H}]\text{glucose}$, 5 $\mu\text{Ci}/\text{ml}$, 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. R_a and R_d 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 ZnSO_4 , 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 Hohorst (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 FI_{O_2} 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 hyperoxic exercise with hypoxic exercise on glucose turnover and counterregulation, base-line to exercise differences in each variable (designated, for example, as ΔR_d) were analyzed using paired t tests. Standard techniques of linear regression were used to assess changes in $\dot{V}\text{O}_2$ and O_2 saturation over the period of the exercise

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

RESULTS

Effect of FI_{O_2} on Lactate Threshold

In all 10 subjects, the lactate threshold occurred at a lower work rate and $\dot{V}O_2$ when the FI_{O_2} was 0.15 compared with 0.21 (mean decrease in $\dot{V}O_2$ at the lactate threshold, 19%; Fig. 1). An additional increase was observed at FI_{O_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. $\dot{V}O_2$ 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 hyperoxic 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 ± 8.1 mg/dl) did not differ from that measured during hyperoxia (92.4 ± 7.9 mg/dl). Glucose concentrations did not change appreciably during hypoxic or hyperoxic exercise. Glucose concentration during hypoxic exercise was 97.6 ± 5.1 mg/dl compared with hyperoxia, 97.4 ± 8.6 mg/dl.

Under hypoxic conditions, mean base-line values of R_d increased from 3.16 ± 1.39 $mg \cdot min^{-1} \cdot kg^{-1}$ to a mean of 5.43 ± 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 ± 1.15 $mg \cdot min^{-1} \cdot kg^{-1}$ to a mean of 4.77 ± 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 ΔR_d during hypoxia was greater than during

hyperoxia by 265%, $P < 0.05$ (Fig. 2). In addition, ΔMCR was significantly greater during hypoxic exercise (Fig. 2). The mean resting MCR during hypoxia was 2.94 ± 1.17 $ml \cdot min^{-1} \cdot kg^{-1}$ and increased to 5.66 ± 2.23 $ml \cdot min^{-1} \cdot kg^{-1}$ during hypoxic exercise. The mean resting MCR during hyperoxia was 4.13 ± 1.17 $ml \cdot min^{-1} \cdot kg^{-1}$ and was 4.84 ± 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 ± 0.95 compared with 3.00 ± 1.28 $mg \cdot min^{-1} \cdot kg^{-1}$), but this difference was not statistically significant. ΔR_a during hypoxic exercise was greater than during hyperoxic exercise in 9 of the 10 subjects. The average ΔR_a during hypoxia was significantly greater than during hyperoxia by 188% (Fig. 2). The mean exercise R_a was 5.56 ± 2.13 $mg \cdot min^{-1} \cdot kg^{-1}$ during hypoxia and 5.27 ± 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 (Δ lactate) and pyruvate (Δ pyruvate) were significantly higher during hypoxic exercise. In addition,

FIG. 2. Mean base-line to exercise increase in glucose uptake (ΔR_d), production (ΔR_a), and metabolic clearance rate (ΔMCR) in response to exercise during hypoxic (hatched bars) and hyperoxic (clear bars) conditions in 10 healthy males. Hypoxia led to significantly greater increases in R_d , R_a , and MCR during exercise than did hyperoxia even though work rate increment was same for both conditions. Shown here are means $\pm$ SE. *Significant difference.

FIG. 1. Effect of FI_{O_2} on lactate (anaerobic) threshold in 10 normal subjects. FI_{O_2} is on the x-axis and $\dot{V}O_2$, in ml O_2 /min, is on the y-axis. $\dot{V}O_2$ corresponding to LT was greater in all 10 subjects at an FI_{O_2} of 0.21 compared with 0.15. A further but generally smaller increase occurred at an FI_{O_2} of 0.80 in 9 of 10 subjects.

FIG. 3. Lactate, pyruvate, and lactate-to-pyruvate ratio (L/P) in response to exercise during hypoxic and hyperoxic conditions. Clear bars represent mean $\pm$ SE of base-line conditions. Hatched bars represent mean $\pm$ SE of increase in each of these variables (Δ lactate, Δ pyruvate, Δ L/P). Δ Lactate, Δ pyruvate, and Δ L/P were all significantly greater during exercise under hypoxic compared with hyperoxic conditions as indicated by asterisk.

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

human subjects can be affected by the O_2 concentration of the inspired gas. During hypoxia, the metabolic demand imposed by the moderate work rates led to significantly larger increases in R_a and R_d than during hyperoxia (Fig. 2). The increased glucose uptake was accompanied by increased concentrations of lactate and pyruvate and larger lactate to pyruvate ratios (Fig. 3), suggesting a mechanism related to changes in the cellular redox state. In addition, our data indicate that the increased glucose production during hypoxia was mediated by elevated levels of catecholamines (Fig. 5).

Glucose uptake can be directly affected by insulin, by blood flow to the tissues, and by the redox state of the cells. It is unlikely that insulin levels were directly responsible for the increased glucose uptake during hypoxic exercise, since the levels of insulin were the same for both hypoxic and hyperoxic exercise (Fig. 3). Muscle blood flow is known to increase with exercise and can be further affected by FI_{O_2} . Welch et al. (31) showed that in exercising subjects breathing 100% O_2 the increase in muscle blood flow was ~10% less than in normoxia. Some investigators have hypothesized that glucose delivery to the muscle (the product of muscle blood flow and glucose concentration) may be an important modulator of muscle glucose uptake (21). Recently, however, Rennie et al. (19) demonstrated in vitro that the glucose transport rate is largely independent of the flow rate during muscular contraction. Thus small differences in blood flow that may have occurred in the present protocol appear unlikely to have been a major determinant of the increase in glucose uptake during hypoxic exercise.

The increase in both lactate and pyruvate was greater under hypoxic conditions as would be expected to result from more rapid glycolysis (mass action effect). But when glucose uptake in muscle tissue is induced by hypoxia, it is accompanied by an increase in the intracellular lactate-to-pyruvate ratio (2, 26). The lactate-to-pyruvate ratio is thought to reflect the cell redox state, i.e., the ratio of NADH to NAD (33). During the 40 min of constant load exercise in the present studies, it is likely that serum values of lactate and pyruvate reflect general trends at the cellular level. Therefore, the elevated lactate-to-pyruvate ratios consistently observed during hypoxic compared with hyperoxic exercise probably indicate a more reduced muscle cell redox state.

The data presented here are consistent with other in vitro and in vivo studies demonstrating that tissue hypoxia can be a critical determinant of glucose uptake. Experiments done in electrically stimulated, perfused rat hindlimb preparations have shown that hypoxic perfusates increase glucose uptake (10, 26). When O_2 availability to exercising muscle is limited by anemia, glucose uptake and production are significantly increased, as recently demonstrated in exercising dogs (29). Finally, hypoxic exercise has been demonstrated to increase splanchnic glucose production in humans (20).

Base-line levels of norepinephrine and epinephrine were unaffected by the gas mixture (Fig. 5). Consistent with previous studies (4), both substances increased during exercise and the increases were greater in the hypoxic state indicating additional adrenergic drive. Although

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

FIG. 5. Norepinephrine and epinephrine in response to exercise during hypoxia and hyperoxia. Clear bars represent mean $\pm$ SE of base-line conditions. Hatched bars represent mean $\pm$ SE of the exercise-induced increase in catecholamines (Δ norepinephrine, Δ 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 FI_{O_2} . Catecholamines have been shown to stimulate R_a even in 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 O_2 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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