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Blood glucose turnover during high- and low-intensity exercise

GLUCOSE UPTAKE; GLUCOSE PRODUCTION; ANAEROBIC THRESHOLD; LACTATE THRESHOLD; CATECHOLAMINES; INSULIN; GAS EXCHANGE

DURING EXERCISE, O_2 UPTAKE (V_O_2) INCREASES IN AN ALMOST LINEAR MANNER WITH WORK RATE (40). IT IS ALSO GENERALLY HELD THAT UPTAKE OF GLUCOSE BY EXERCISING MUSCLES INCREASES WITH WORK RATE (32, 38). HOWEVER, THERE ARE A NUMBER OF REASONS TO BELIEVE THAT WHOLE BODY GLUCOSE TURNOVER MIGHT NOT PARALLEL THE V_O_2 RESPONSE TO EXERCISE.

GLUCOSE UPTAKE DURING EXERCISE IS NOT RELATED IN A SIMPLE, LINEAR MANNER TO O_2 UPTAKE (V_O_2). TO TEST THIS, SEVEN HEALTHY MALE SUBJECTS (AGE RANGE 23-34 YR) WERE STUDIED IN THE POSTABSORPTIVE BUT NOT GLYCOGEN-DEPLETED STATE. THREE CONDITIONS WERE EXAMINED: 1) REST, 2) 40 MIN OF CONSTANT EXERCISE IN WHICH THE WORK RATES WERE CAREFULLY CHOSEN TO CONSIST OF LOW-INTENSITY EXERCISE (NO ELEVATED BLOOD LACTATE, A MEAN OF 40% MAXIMAL V_O_2), AND 3) 40 MIN OF HIGH-INTENSITY EXERCISE (MARKEDLY ELEVATED BLOOD LACTATE, 79% MAXIMAL V_O_2). GAS EXCHANGE WAS MEASURED BREATH BY BREATH, AND GLUCOSE UPTAKE AND PRODUCTION WERE MEASURED USING [6,6-2H_2]GLUCOSE. LOW INTENSITY EXERCISE (N = 7) RESULTED IN A SMALL BUT NOT STATISTICALLY SIGNIFICANT INCREASE IN MEAN R_d [3.06 ± 0.37 (SE) mg·min⁻¹·kg⁻¹] COMPARED WITH RESTING VALUES (2.87 ± 0.39 mg·min⁻¹·kg⁻¹) DESPITE A FOURFOLD INCREASE IN THE PRODUCTION OF CO_2 AND V_O_2. BY CONTRAST, THE HIGH-INTENSITY EXERCISE R_d (N = 5, 6.98 ± 0.67 mg·min⁻¹·kg⁻¹) WAS SIGNIFICANTLY GREATER THAN THE RESTING VALUE (3.03 ± 0.56 mg·min⁻¹·kg⁻¹). RESULTS OF GLUCOSE PRODUCTION WERE VIRTUALLY THE SAME. SIMILARLY, MEAN LEVELS OF EPINEPHRINE AND NOREPINEPHrine INCREASED SIGNIFICANTLY ABOVE RESTING VALUES DURING HIGH- BUT NOT LOW-INTENSITY EXERCISE. OUR DATA DEMONSTRATE THAT WHOLE BODY GLUCOSE DYNAMICS AND REGULATION DURING 40 MIN OF EXERCISE DO NOT CHANGE IN A SIMPLE LINEAR MANNER WITH RESPECT TO METABOLIC RATE.

METHODS

POPULATION. THE STUDY POPULATION CONSISTED OF SEVEN HEALTHY MALES RANGING IN AGE FROM 23 TO 34 YR OLD. AGE, WEIGHT, HEIGHT, AND PARAMETERS OF AEROBIC EXERCISE ARE SHOWN IN TABLE 1. IT IS NOTEWORTHY THAT THE POPULATION WAS GENERALLY FIT AS JUDGED BY THE RATIO OF ANAEROBIC THRESHOLD (AT) TO MAXIMAL V_O_2 (V_O_2max AND V_O_2max PER KILOGRAM. THE PROJECT WAS APPROVED BY THE INSTITUTIONAL REVIEW BOARD FOR HUMAN SUBJECTS AND INFORMED CONSENT WAS OBTAINED.

PROTOCOL. EACH SUBJECT PERFORMED A PROGRESSIVE EXERCISE TEST (RAMP PROTOCOL) ON A CYCLE ERGOMETER FOR THE DETERMINATION OF THE V_O_2max AND THE LACTATE AT AT (41). THE
AT is used to determine the work rate above which lactate increases the blood. Based on these progressive exercise tests, two work rates were chosen for the constant work rate exercise protocol: low intensity work rate was comparable to ~60% of the subject's AT, and high intensity work was comparable to 25% of the difference between the AT and the VO$_2$ max. These work rates were chosen so that low-intensity exercise would result in a significant and easily measurable increase in VO$_2$ while exercise performed above the AT would not be too difficult for the subjects to perform continuously for 40 min as required by the protocol. These work rates represented $40 \pm 4\%$ (SE) and $79 \pm 4\%$ VO$_2$ max for the low- and high-intensity exercise, respectively. Two of the subjects experienced mild vasovagal symptoms during the rest period before the high-intensity exercise protocols, and the tests were discontinued. Thus seven subjects completed the low-intensity exercise, and five of them completed the high-intensity protocol as well.

Each exercise testing session (viz, progressive exercise, low-intensity constant work rate exercise, and high-intensity constant work rate exercise) occurred on separate mornings after an overnight fast. The exercise sessions were separated by at least 1 wk, and whether the work rate would be high or low intensity was determined by the flip of a coin. In the constant work rate protocols, each subject received a priming dose of [6,6-$^3$H$_2$]glucose, and a constant infusion of the tracer was begun via catheterization of an antecubital vein. We chose [6,6-$^3$H$_2$]glucose because it had been previously used as a tracer for measurements of whole body glucose turnover (6) and because glucose recycling pathways have little quantitative effect on hydrogen atoms in the sixth position of the molecule (5, 23). The constant infusion was calculated individually for each subject to achieve ~2-3% labeling of peripheral blood glucose under resting conditions (mean priming dose of 6.28 mg/kg and mean infusion rate of 0.079 mg·kg$^{-1}$·min$^{-1}$). Based on our previous studies of glucose turnover (11), we used the value of 3 mg·min$^{-1}$·kg$^{-1}$ as the target glucose uptake to ensure a measurable enrichment for both rest and exercise. The bolus or priming dose was determined as the amount of labeled glucose equivalent to the first 80 min of tracer infusion. One hundred minutes were used for achievement of steady-state enrichment. The measurement period followed and consisted of 40 min of rest and then 40 min of constant work rate exercise. Blood samples were obtained from a catheterized antecubital vein every 5 min for glucose concentration and isotopic enrichment and every 10 min for measurement of lactate (18), IRI (15), epinephrine, and norepinephrine (29).

Plasma samples were deproteinized and gasoline was isolated using standard techniques. The aldonitrile pentaacetate derivative of glucose was used to assess enrichment of glucose using electron beam ionization and gas chromatography-mass spectrometry (36, 37). Isotopic enrichment was calculated using a least-squares approach (25), which allowed us to measure the molar isotopic ratio. Tracer was assumed to mix with tracee within a single glucose compartment using modifications described by Steele (35). The rate of glucose appearance ($R_a$, i.e., hepatic glucose production) and the rate of glucose disappearance ($R_d$) were calculated by knowing the rate of infusion and by measuring glucose concentration and the ratio of labeled to unlabeled glucose. These calculations have been validated during conditions of non-steady-state glucose flux (30).

**TABLE 1. Age, weight, aerobic parameters, and work rate during constant exercise in study sample**

| Subject | Age, yr | Weight, kg | VO$_2$max, l/min | AT, l/min | AT/VO$_2$max | VO$_2$max/kg, ml·min$^{-1}$·kg$^{-1}$ | AT/kg, ml·min$^{-1}$·kg$^{-1}$ | Low-Intensity Work Rate, W | High-Intensity Work Rate, W | Low-Intensity VO$_2$, %VO$_2$max | High-Intensity VO$_2$, %VO$_2$max |
|---------|---------|------------|------------------|-----------|--------------|-----------------------------------|-------------------------------|-----------------------------|----------------------------------|--------------------------------|----------------------------------|
| 1       | 24      | 84         | 4.95             | 2.05      | 48           | 51                                               | 24                           | 65                          | 32                               |                                 |
| 2       | 27      | 76         | 4.49             | 3.22      | 72           | 59                                               | 42                           | 115                         | 39                               |                                 |
| 3       | 23      | 65         | 3.33             | 2.09      | 59           | 54                                               | 32                           | 70                          | 165                              | 32                              | 72                               |
| 4       | 30      | 67         | 4.41             | 2.90      | 66           | 66                                               | 43                           | 110                         | 230                              | 32                              | 69                               |
| 5       | 29      | 74         | 3.40             | 2.58      | 76           | 46                                               | 35                           | 75                          | 183                              | 33                              | 72                               |
| 6       | 23      | 87         | 2.65             | 1.77      | 67           | 31                                               | 20                           | 85                          | 163                              | 66                              | 86                               |
| 7       | 34      | 76         | 3.30             | 1.84      | 56           | 43                                               | 24                           | 90                          | 210                              | 47                              | 94                               |

Means±SE 27±1 76±3 3.72±0.24 2.35±0.20 63±3 50±4 32±3 87±7 190±10 40±4 79±4

* Anerobic threshold per kilogram.
TABLE 2. Mean \( \dot{V}O_2 \), \( \dot{V}CO_2 \), and HR during rest and low- and high-intensity exercise

| Subject | \( \dot{V}O_2 \) l/min | \( \dot{V}CO_2 \) l/min | HR, beats/min |
|---------|------------------------|------------------------|--------------|
|         | Rest                   | Low-intensity exercise | Rest         | Low-intensity exercise | High-intensity exercise | Rest         | Low-intensity exercise | High-intensity exercise |
| 1       | 0.37                   | 1.37                   | 0.30         | 1.04                   |                   | 68           | 90                       |
| 2       | 0.27                   | 1.73                   | 0.19         | 1.60                   |                   | 61           | 98                       |
| 3       | 0.35                   | 1.12                   | 0.28         | 0.99                   | 0.30             | 2.23         | 0.26         | 1.99                   | 0.30             | 2.28         | 0.26         | 1.89                   |
| 4       | 0.47                   | 1.74                   | 0.23         | 1.01                   | 0.32             | 2.28         | 0.31         | 1.33                   | 0.31             | 2.30         | 0.31         | 1.53                   |
| 5       | 0.47                   | 1.54                   | 0.22         | 1.36                   | 0.36             | 3.15         | 0.23         | 1.47                   | 0.31             | 2.29         | 0.30         | 2.28                   |
| 6       | 0.47                   | 1.54                   | 0.22         | 1.36                   | 0.36             | 3.15         | 0.23         | 1.47                   | 0.31             | 2.29         | 0.30         | 2.28                   |
| 7       | 0.34                   | 1.54                   | 0.22         | 1.36                   | 0.36             | 3.15         | 0.23         | 1.47                   | 0.31             | 2.29         | 0.30         | 2.28                   |

Means 0.35±0.02, 1.43±0.09*, 0.41±0.02, 2.63±0.15†, 0.26±0.02, 1.26±0.09*, 0.33±0.01, 2.59±0.18†, 66±3, 101±4*, 68±4, 157±8†

\( \dot{V}O_2 \), \( O_2 \) uptake; \( \dot{V}CO_2 \), \( CO_2 \) output; HR, heart rate. * Significantly greater than rest (\( P < 0.01 \)). † Significantly greater than rest and low-intensity exercise (\( P < 0.01 \)).

FIG. 2. Blood glucose and lactate concentrations during rest and high- and low-intensity exercise. Closed triangles, high-intensity protocol; open squares, low intensity protocol. Data points, mean ± SE at each sampling interval. There were no significant differences in glucose concentrations among rest and high- and low-intensity exercise. Mean lactate during low-intensity exercise was virtually unchanged from rest but was markedly increased during high-intensity exercise.

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 partial pressure of \( O_2 \) (\( PO_2 \)) and \( CO_2 \) (\( PCO_2 \)) were determined by mass spectrometry from a sample drawn continuously from the mouthpiece at 1 ml/s. The electrical signals from these devices underwent analog-to-digital conversion for the on-line breath-to-breath computation of \( \dot{V}O_2 \) (STPD), \( CO_2 \) output (\( \dot{V}CO_2 \) STPD), and expired ventilation (\( V_e \), BTPS) as previously described (4). HR was measured beat-by-beat using a modified lead I ECG for which three leads were placed on the chest.

Determination of the anaerobic or lactate threshold from gas exchange measurements is well described (42). 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 \( \dot{V}O_2 \). Thus the threshold is measured by finding hyperventilation relative to \( \dot{V}O_2 \) (but not to \( \dot{V}CO_2 \)), i.e., the \( \dot{V}O_2 \) above which \( V_e/\dot{V}O_2 \) and end-tidal \( PO_2 \) increase without an increase in \( V_e/\dot{V}CO_2 \) or a decrease in end-tidal \( PCO_2 \).

Data analysis. The test statistics consisted of the mean values for each subject of the resting and exercise measurements of the variables listed above. Analysis of variance (ANOVA) (repeated measures) was used to test the effect of the different conditions (rest, low-intensity exercise, high-intensity exercise). In the cases where missing data were present (i.e., the two subjects who did not complete the high-intensity protocol), iterative techniques were used to estimate these values (34). Moreover, statistical analysis of the five subjects who completed all protocols was invariably the same as using the seven subjects. When ANOVA was significant, mean values were compared with modified \( t \) tests. Values are expressed as the mean ± SE.

RESULTS

Gas exchange and heart rate responses. An example of a typical \( \dot{V}O_2 \) and HR response to the constant work rate protocol is shown in Fig. 1. In this subject, regression analysis of \( \dot{V}O_2 \) and HR during the high-intensity exercise period showed that both \( \dot{V}O_2 \) and HR increased progressively with time (\( r = 0.42 \), \( P < 0.05 \) and \( r = 0.91 \), \( P < 0.05 \), respectively) despite the fact that the work rate was constant; this observation is characteristic of exercise performed above the AT as demonstrated in previous studies (8). The mean values of \( \dot{V}O_2 \), \( \dot{V}CO_2 \), and HR obtained from the 40 min of low-intensity exercise were significantly greater than the mean values during the 40-min rest period (Table 2) (e.g., below-AT exercise resulted in a fourfold increase in mean \( \dot{V}O_2 \) over resting values). The mean values of \( \dot{V}O_2 \), \( \dot{V}CO_2 \), and HR from high-intensity exercise were significantly greater than
Glucose turnover. The mean values for glucose and lactate concentrations are shown in Fig. 2. Figure 3 shows the molar isotopic enrichment of glucose and the calculated values for $R_a$ and $R_d$ at each sampling interval during the rest and exercise portions of the protocol. As expected, lactate concentrations did not change between rest and low-intensity exercise (mean lactate, 0.70 ± 0.05 mM and 0.79 ± 0.07 mM, respectively) but were significantly higher during high-intensity exercise (mean 3.11 ± 0.66 mM, $P < 0.01$ compared with resting values).

We calculated the possibility of a type 2 statistical error (i.e., the probability that there was, in fact, an increase in glucose turnover between rest and low-intensity exercise). For a true 10% increase the probability of a type 2 error is 0.5; it drops to 0.15 or less for a true 20% difference and is <0.10 for an increase of 30%. Moreover, given the variance of the data, a sample population of 117 would have been required to achieve statistical significance ($P < 0.05$) for the 7% increase in glucose that we actually observed between rest and low-intensity exercise (13).

Norepinephrine, epinephrine, and insulin. It can be seen in Fig. 4 that there was no significant difference in norepinephrine concentrations between rest and low-intensity exercise (mean 438 ± 53 and 553 ± 60 pg/ml, respectively); however, norepinephrine was significantly elevated at high-intensity exercise (mean value 2142 ± 417 pg/ml, $P < 0.01$ greater than resting values). Although levels of epinephrine increased during low-intensity exercise (mean values: rest, 31 ± 4 pg/ml; below AT, 63 ± 6) only during high-intensity exercise (mean value, 180 ± 43 pg/ml) did the increase achieve statistical significance ($P < 0.01$). It is noteworthy that regression analysis during the low-intensity exercise identified a significant upward trend of the mean epinephrine concentration as the exercise period progressed ($r = 0.94, P < 0.05$).

The mean values of IRI during rest (6.0 ± 1.0 μU/ml) and low- (4.5 ± 1.1) and high-intensity exercise (4.0 ± 0.6) were not statistically different. Nonetheless, during exercise IRI tended to fall from resting values (Fig. 4) with regression analysis over time showing correlations of -0.66 ($P < 0.05$) and -0.89 ($P < 0.05$) for low and high-intensity exercise, respectively.

**DISCUSSION**

The data suggest that high-intensity exercise (in the range of work rates associated with elevated lactate concentrations) is associated with a different pattern of glucose production, utilization, and regulation than is low-intensity exercise (no increase in lactate concentra-
tions). We found no statistically significant increase in mean Rₐ and Rₜ during low-intensity exercise compared with resting values. However, even if a small increase in glucose uptake was missed (a type 2 error), the analysis of our data virtually precludes the magnitude of this increase to be anywhere near the fourfold increase in V̇O₂. By contrast, glucose turnover increased markedly during high-intensity exercise. The data presented here document work-rate related differences in glucose turnover and catecholamine responses that parallel the differences in blood lactate concentrations known to occur above and below the lactate or AT. Although our data do not definitively demonstrate a threshold for glucose uptake and production during exercise, these findings do support the hypothesis that whole body glucose turnover is not related in a simple linear manner to metabolic rate (V̇O₂).

The results of this study are not inconsistent with previous investigations. We examined a group of studies done since 1980 in which whole body blood glucose turnover was measured during exercise in humans with the use of metabolic tracers (9, 11, 16, 20, 21, 28, 33, 44) (Table 4). In Fig. 5, the mean data from each of these studies are plotted along with the results of the present study and the data on leg glucose uptake obtained by Wahren and co-workers (38). The whole body glucose uptake data from the other laboratories suggest a nonlinear increase in glucose uptake at work rates occurring between 40 and 60% of V̇O₂max. This is the range of work rates where the anaerobic or lactate threshold normally occurs.

As can be seen in Fig. 5, our study differs from that of Wahren et al. (38) in which blood glucose uptake across exercising muscles was estimated from estimates of leg blood flow and measurements of glucose concentrations obtained with arterial and venous femoral catheters. We did not observe a significant increase in Rₐ or Rₜ from rest to below-AT exercise, whereas Wahren’s group demonstrated a sevenfold increase in glucose uptake from rest to 65-W exercise. Resting glucose uptake measured in the other investigations of whole body glucose uptake was also markedly different from Wahren’s data. This apparent discrepancy may actually reflect the fact that local muscle glucose uptake is not necessarily proportional to whole body glucose kinetics. In the transition between rest and exercise, cardiac output is redistributed; blood flow to the working muscles increases while blood flow to other tissues remains constant or actually falls (10). Therefore an increase in muscle glucose uptake during exercise could be balanced by reduction in glucose uptake by other tissues due, in part, to the reduced delivery of glucose to these tissues (e.g., to adipose tissue or nonexercising muscle). As a result, Rₐ and Rₜ (measured by tracer dilution and reflecting whole body glucose kinetics) during low-intensity exercise need not change in direct proportion to the changes occurring at the exercising muscles.

There are, however, certain qualitative similarities between our findings and the observations of Wahren’s group (38). In their study, a 65-W increase in work rate (from 65 to 130 W) resulted in only a 43% increase in muscle glucose uptake, whereas an additional 64-W increase in work rate resulted in a doubling of glucose uptake. The difference between leg and whole body glucose uptake appears to be virtually gone by light exercise (10).

| Subject | Rest | Low-Intensity Exercise | Rest | High-Intensity Exercise | Rest | Low-Intensity Exercise | Rest | High-Intensity Exercise |
|---------|------|------------------------|------|-------------------------|------|------------------------|------|-------------------------|
|         |      |                        |      |                         |      |                        |      |                         |
|         |      | Glucose concentration, mg/100 mg |      |                         |      | Glucose concentration, mg/100 mg |      |                         |
| 1       | 73.0 | 72.9                   | 3.05 | 3.14                    | 5.45 | 5.63                   | 7.65 | 7.87                    |
| 2       | 90.0 | 90.4                   | 1.83 | 1.86                    | 3.99 | 4.03                   | 5.03 | 5.02                    |
| 3       | 87.5 | 90.9                   | 1.94 | 2.00                    | 6.38 | 6.43                   | 8.73 | 8.77                    |
| 4       | 86.5 | 91.2                   | 1.67 | 1.50                    | 5.28 | 5.33                   | 7.07 | 7.12                    |
| 5       | 92.8 | 100.8                  | 2.32 | 2.38                    | 6.03 | 6.08                   | 7.86 | 7.92                    |
| 6       | 86.8 | 94.0                   | 2.57 | 2.56                    | 5.98 | 6.03                   | 7.86 | 7.92                    |
| 7       | 90.6 | 104.3                  | 2.22 | 2.28                    | 5.03 | 5.06                   | 6.98 | 6.96                    |
|         |      | Molar isotopic ratio, % |      |                         |      | Molar isotopic ratio, % |      |                         |
| 1       |      | 1.34                   |      | 1.42                    |      | 2.59                   |      | 2.61                    |
| 2       |      | 3.99                   |      | 4.40                    |      | 5.22                   |      | 5.65                    |
| 3       |      | 2.41                   |      | 2.12                    |      | 3.83                   |      | 3.36                    |
| 4       |      | 4.43                   |      | 3.30                    |      | 5.60                   |      | 5.35                    |
| 5       |      | 3.14                   |      | 2.22                    |      | 3.43                   |      | 3.26                    |
| 6       |      | 2.88                   |      | 2.32                    |      | 3.30                   |      | 3.22                    |
| 7       |      | 2.63                   |      | 2.65                    |      | 3.53                   |      | 3.12                    |

Rₐ, glucose production; Rₜ, glucose uptake. * Differed significantly from resting, P < 0.05.
GLUCOSE TURNOVER DURING EXERCISE

It is important to note that glucose turnover during even moderate exercise is likely to be dependent on the duration of the exercise and on the work intensity. As glycogen is progressively depleted in postabsorptive sub-

exponential increase in glucose uptake with increasing work rate (Fig. 5).

It is important to note that glucose turnover during even moderate exercise is likely to be dependent on the duration of the exercise and on the work intensity. As glycogen is progressively depleted in postabsorptive sub-

FIG. 4. Epinephrine, norepinephrine, and immunoreactive insulin (IRI) during rest and high- and low-intensity exercise. Closed triangles, high intensity protocol; open squares, low-intensity protocol. Data points, mean ± SE at each sampling interval. Mean values of both epinephrine and norepinephrine during high-intensity exercise were markedly increased compared with mean resting values. Mean norepinephrine during low-intensity exercise was not greater than mean resting value. Although mean epinephrine during low-intensity exercise did not differ from mean resting value, linear regression analysis over time demonstrated that epinephrine significantly increased in low-intensity protocol. Mean IRI during high- and low-intensity exercise did not differ from the mean resting values. However, linear regression analysis over time showed that IRI tended to decrease with time during both protocols.

FIG. 5. Glucose uptake (mmol/min) during exercise as a function of metabolic rate (% $\overline{V}O_2$,$\max$). Open circles, mean values of data of this study; triangles, data from Wahren et al. (38), and closed circles, data from 7 studies cited in Table 4 (excluding our previous study on exercise during hypoxia). For Wahren’s study and investigations cited in Table 4, we used the mean value during exercise period (exercise periods ranged from 40 to 60 min). Resting values for the 7 cited studies (closed circles) was the average of all 7 studies. Wahren et al. did not provide $\overline{V}O_2$,$\max$ data for subjects. However, age, height, and weight data on Wahren’s subjects were provided in an accompanying paper (14), and these values were used to predict $\overline{V}O_2$,$\max$ (40). Note discrepancy between leg glucose uptake (Wahren’s data) and whole body glucose uptake under resting conditions. Whole body glucose uptake data suggest a step increase in glucose uptake occurring between 40 and 60% of $\overline{V}O_2$,$\max$. Our data, in combination with those of Wahren, suggest an almost exponential increase in glucose uptake as metabolic rate approaches $\overline{V}O_2$,$\max$. The data support, therefore, the strong association of norepinephrine and epinephrine release with glucose production to meet the increased uptake of blood glucose during high-intensity exercise. In contrast, IRI was not closely associated with the changes in $R_d$ and $R_b$, and the mean values of IRI during low and high-intensity exercise did not differ. The data suggest, therefore, that regulation of IRI, although physiologically significant during exercise, is not proportionally related to work.
protocols are designed using a fixed percentage of the
be a mixed sample population with subjects exercising
precise range in which the lactate threshold is known to
occur (42), in virtually none of the studies was the lactate
any population of normal subjects. When work rate
in part, different levels of fitness (12) encountered in
uals and 50-70% in our sample). This variability reflects,
perfusates were used in isolated perfused rat hindlimb
both below and above the lactate threshold. Moreover,
40 and 60% of the subject's Tjozmax. Although this is the
measurement of VO2max "is the method of choice for any
scientific investigation." Thus it is not surprising that in
a number of the studies cited in Table 4, the investigators
actually had to lower the work rate of some subjects
while exercise was in progress because HRs were contin-
ously increasing and subjects were experiencing fatigue.

A distinguishing feature of high-intensity (above-AT)
exercise may be the presence of hypoxia at the muscle
tissue level. In a recent review, Katz and Sahlin (24)
concluded that lactate production during submaximal
exercise was "O2 dependent." Randle and Smith (31)
demonstrated in 1958 that hypoxia is a major stimulus
of glucose uptake in the rat diaphragm in vitro, thereby
establishing the existence of a "Pasteur effect" in mam-
malian muscle cells. More recently, Bylund-Fellenius et
al. (7), using intramuscular PO2 probes, demonstrated
marked increases in muscle glucose uptake as tissue PO2
tell in exercising humans, and Idstrom and co-workers
(19) showed increases in glucose uptake when hypoxic
perfusates were used in isolated perfused rat hindlimb
experiments. Finally, Wasserman and co-workers (39)
found that blood glucose uptake and production in-
creased in exercising dogs when O2 flow to the working
muscles was reduced by anemia.

However, regardless of the underlying mechanism re-
sponsible for the increase in lactate concentrations above
the lactate threshold, we believe that distinguishing high-
from low-intensity exercise is functionally important in
understanding the metabolic adaptation to exercise. In
earlier studies of peripheral blood glucose turnover dur-
ing exercise in humans, two- to fourfold increases in
glucose uptake were usually reported. We wondered
whether the discrepancy between these studies and our
findings during low-intensity work arose from differences
in the choice of work rate protocols in the various studies.
In examining the studies reviewed in Table 4, we were
struck by the observation that the work rate chosen for
the experimental protocol was almost invariably between
40 and 60% of the subject's VO2 max. Although this is the
precise range in which the lactate threshold is known to
occur (42), in virtually none of the studies was the lactate
threshold measured.

The lactate threshold can occur over a relatively large
range (as noted, 40-60% of VO2 max in sedentary individ-
uals and 50-70% in our sample). This variability reflects,
in part, different levels of fitness (12) encountered in
any population of normal subjects. When work rate
protocols are designed using a fixed percentage of the
VO2 max in the range of 40-60%, the result will invariably
be a mixed sample population with subjects exercising
both below and above the lactate threshold. Moreover,
most of the studies cited in Table 4 relied on predicted
rather than measured VO2 max, which introduces substan-
tial error in the assessment of the relative work intensity
actually performed by the subjects. It is noteworthy that
Astrand and Rodahl (3), whose predictive nomograms
for VO2 max are most often used, stated that direct meas-
urement of VO2 max "is the method of choice for any
scientific investigation." Thus it is not surprising that in
a number of the studies cited in Table 4, the investigators
actually had to lower the work rate of some subjects
while exercise was in progress because HRs were contin-
uously increasing and subjects were experiencing fatigue.

Inferences can be drawn from our data about the
degree to which peripheral blood glucose contributes to
total energy metabolism during exercise in normal, not
glycogen depleted, subjects by calculating the ratio of the
glucose uptake (Rg) to the metabolic rate (VO2). This is
done by converting Rg and VO2 to equivalent moles of
CO2. If it is assumed that all of the measured glucose
uptake (Rg) were oxidized to CO2, then the ratio of Rg
to VO2 represents the largest contribution that could pos-
sibly be made by glucose in the peripheral blood to the
total amount of oxidized substrate. At rest, this value is
44%. By contrast, for both low- and high-intensity ex-
cise, peripheral blood glucose oxidation could account
for a small proportion of VO2, 12 and 15%, respectively,
reflecting the fact that the metabolic rate changes much
more markedly than does Rg during exercise. Thus glu-
cose stored in the peripheral blood tends to be conserved
during exercise periods lasting as long as 40 min, and
 glucose uptake and production appear to increase in a
nonlinear manner as work rate increases in intensity.

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REFERENCES
1. AHLBORG, G., P. FELIG, L. HAGENFELDT, R. HENDLER, AND J.
WAHREN. Substrate turnover during prolonged exercise in man. J.
Clin. Invest. 53: 1080-1090, 1974.
2. ANDRES, R., G. CADEr, AND K. L. ZIERLER. The quantitatively
minor role of carbohydrate in oxidative metabolism by skeletal

| Year   | Protocol Work Rate | VO2max | AT or LT Measured | Constant or Work Rate | Simultaneous VO2 or HR Measurement | Tracer Ref. No. |
|--------|--------------------|--------|-------------------|-----------------------|-----------------------------------|-----------------|
| 1980   | 50-60% VO2max      | Predicted* | No                | Constant              | VO2 and HR                        | [3-3H]glucose 28 |
| 1982   | 30% VO2max         | Predicted* | No                | Variable†             | VO2 and HR                        | [3-3H]glucose 44 |
| 1982   | 60% VO2max         | Predicted* | No                | Variable†             | HR only                           | [3-3H]glucose 9  |
| 1994   | 40% VO2max         | Measured | No                | Variable†             | Not stated                        | [3-3H]glucose 33 |
| 1986   | 60% VO2max         | Predicted* | No                | Variable†             | VO2 and HR                        | [3-3H]glucose 20 |
| 1986   | 50-60% VO2max      | Measured | No                | Constant              | VO2 and HR                        | [3-3H]glucose 16 |
| 1986   | Above and below AT | Measured | Yes               | Constant              | VO2 and HR                        | [3-3H]glucose 11 |
| 1986   | 55% VO2max         | Predicted* | No                | Variable†             | HR only                           | [2-1H]glucose 21 |
museum in intact man, in the basal state. J. Clin. Invest. 35: 671–682, 1966.

2. Åstrand, P.-O., and K. Rodahl. Textbook of Work Physiology: Physiological Bases of Exercise (2nd ed.). New York: McGraw-Hill, 1977.

3. Beaver, W. L., N. Lamarr, and K. Wasserman. Breath-by-breath measurement of true alveolar gas exchange. J. Appl. Physiol. 51: 1662–1675, 1981.

4. Biel, D. M., K. J. Arnold, W. R. Shierman, W. H. Holland, W. F. Holmes, and D. M. Kipnis. In vivo measurements of glucose and alanine metabolism with stable isotope tracers. Diabetes 26: 1005, 1977.

5. Biel, D. M., D. R. Leake, M. W. Raymond, K. J. Arnold, L. D. Gruenke, M. A. Sperling, and D. M. Kipnis. Measurement of "true" glucose production rates in infancy and childhood with 6,6 diasteroergulose. Diabetes 26: 1016–1023, 1977.

6. Dylund-Fellenius, A., P. M. Walker, A. Elander, S. Holm, J. Holm, and T. Schersten. Energy metabolism in relation to oxygen partial pressure in human skeletal muscle during exercise. Biochem. J. 200: 247–255, 1981.

7. Casaburi, R., T. W. Storer, I. Ben-Dov, and K. Wasserman. Effect of endurance training on possible determinants of VO₂ during heavy exercise. J. Appl. Physiol. 52: 399–407, 1982.

8. Chisholm, D. J., A. B. Jenkins, D. E. James, and E. W. Kraegen. The effect of hyperinsulinaemia on glucose homeostasis during moderate exercise in man. Diabetes 31: 603–608, 1982.

9. Clement, D. L., and J. T. Shepherd. Regulation of peripheral circulation during muscular exercise. Prog. Cardiovasc. Dis. 19: 23–31, 1976.

10. Cooper, D. M., D. H. Wasserman, M. Vranic, and K. Wasserman. Glucose turnover in response to exercise during high- and low-VO₂, breathing in man. Am. J. Physiol. 251 (Endocrinol. Metab. 14): E209–E214, 1986.

11. Davis, J. A., M. H. Frank, B. J. Whipp, and K. Wasserman. Anorexic threshold alterations caused by endurance training in middle-aged men. J. Appl. Physiol. 46: 1039–1046, 1979.

12. Dixon, W. J., and F. J. Massey. Introduction to Statistical Analysis (3rd ed.). New York: McGraw-Hill, 1969, p. 263–262.

13. Felic, P., and J. Wahren. Amino acid metabolism in exercising man. J. Clin. Invest. 50: 2705–2714, 1971.

14. Herbert, V., K. S. Lau, C. W. Gottfler, and S. Bleicher. Coated charcoal immunoassay of insulin. J. Clin. Endocrinol. Metab. 25: 1370–1378, 1960.

15. Hoezler, D. R., G. P. Dalsky, W. E. Clutter, S. D. Shah, J. O. Holloszy, and P. E. Cryer. Glucose regulation during exercise: hypoglycemia is prevented by redundant glycogenolytic systems, sympatho-chromaffin activation, and changes in islet hormone secretion. J. Clin. Invest. 77: 212–221, 1985.

16. Hoezler, D. R., G. P. Dalsky, N. S. Schwartz, W. E. Clutter, S. D. Shah, J. O. Holloszy, and P. E. Cryer. Epinephrine is not critical to prevention of hypoglycemia during exercise in humans. Am. J. Physiol. 251 (Endocrinol. Metab. 14): E104–E110, 1986.

17. Hohorst, H. J. Lactate assay. In: Methods of Enzymatic Analysis, edited by H. U. Bernmeyer. New York: Academic, 1962, p. 250–270.

18. Inomoto, J., J. F. H. Surraumania, R. Chanfa, T. Schersten, and A. C. Dylund-Fellenius. Oxygen dependence of energy metabolism in contracting and recovering rat skeletal muscle. Am. J. Physiol. 248 (Heart Circ. Physiol. 17): H40–H48, 1965.

19. Jenkins, A. B., D. J. Chisholm, D. E. James, K. Y. Ho, and E. W. Kraegen. Exercise-induced hepatic glucose output is precisely sensitive to the rate of systemic glucose supply. Metabolism 34: 431–436, 1985.

20. Jenkins, A. B., S. M. Furler, D. J. Chisholm, and E. W. Kraegen. Regulation of hepatic glucose output during exercise by circulating glucose and insulin in humans. Am. J. Physiol. 250 (Regulatory Integrative Comp. Physiol. 19): R411–R417, 1986.

21. Jørgensen, L., and J. Wahren. Leg blood flow during exercise in man. Clin. Sci. Lond. 14: 459–468, 1971.