UC Irvine

UC Irvine Previously Published Works

Title

Blood glucose turnover during high- and low-intensity exercise.

Permalink

<https://escholarship.org/uc/item/27x0r99d>

Journal

The American journal of physiology, 257(3 Pt 1)

ISSN

0002-9513

Authors

Cooper, DM
Barstow, TJ
Bergner, A
et al.

Publication Date

1989-09-01

DOI

10.1152/ajpendo.1989.257.3.e405

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Blood glucose turnover during high- and low-intensity exercise

DAN M. COOPER, THOMAS J. BARSTOW, ANNE BERGNER, AND W.-N. PAUL LEE
*Department of Pediatrics, Harbor-University of California at Los Angeles Medical Center,
Torrance, California 90509*

COOPER, DAN M., THOMAS J. BARSTOW, ANNE BERGNER, AND W.-N. PAUL LEE. *Blood glucose turnover during high- and low-intensity exercise*. *Am. J. Physiol.* 257 (Endocrinol. Metab. 20): E405–E412, 1989.—We hypothesized that whole body glucose uptake (R_d) during exercise is not related in a simple, linear manner to O_2 uptake ($\dot{V}O_2$). 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 $\dot{V}O_2$), and 3) 40 min of high-intensity exercise (markedly elevated blood lactate, 79% maximal $\dot{V}O_2$). 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) $mg \cdot min^{-1} \cdot kg^{-1}$] compared with resting values (2.87 ± 0.39 $mg \cdot min^{-1} \cdot kg^{-1}$) despite a fourfold increase in the production of CO_2 and $\dot{V}O_2$. By contrast, the high-intensity exercise R_d ($n = 5$, 6.98 ± 0.67 $mg \cdot min^{-1} \cdot kg^{-1}$) was significantly greater than the resting value (3.03 ± 0.56 $mg \cdot min^{-1} \cdot kg^{-1}$). 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.

glucose uptake; glucose production; anaerobic threshold; lactate threshold; catecholamines; insulin; gas exchange

DURING EXERCISE, O_2 uptake ($\dot{V}O_2$) 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 $\dot{V}O_2$ response to exercise.

Most notably, there is evidence suggesting that substrate utilization is different for strenuous (high-intensity) exercise compared with exercise at more moderate work rates. First, lactate concentrations are increased during exercise only when the work performed is above a certain intensity; exercise performed below this point is not accompanied by changes in blood lactate (26, 43). Second, with exercise of sufficient intensity, breathing hypoxic gas leads to elevated lactate concentrations (which would otherwise only result from increasing the work rate) and to increased rates of glucose uptake and production (11). Third, studies of substrate utilization of leg muscles during exercise also suggest that muscle

glucose uptake does not change as a linear function of work rate. The data of Wahren et al. (38) show that the magnitude of the increase in leg muscle glucose uptake is greater at higher work rates. Finally, it is noteworthy that cardiorespiratory indicators of metabolic rate [e.g., $\dot{V}O_2$, respiratory quotient, and heart rate (HR)] do not achieve steady states when exercise is performed above a certain intensity (viz., when lactate concentrations are elevated) despite the fact that the work rate may remain constant (Fig. 1) (8).

It is also likely that there is a difference, particularly under resting conditions, between glucose turnover of the whole body and glucose turnover of muscle. This discrepancy arises because resting muscle metabolizes relatively little circulating glucose (2) and because resting muscle blood flow and $\dot{V}O_2$ comprise only a small proportion of total cardiac output and $\dot{V}O_2$ (22). As a result, the relationship between whole body glucose uptake and $\dot{V}O_2$ during exercise will be determined, in part, by the proportional redistribution of cardiac output and substrate utilization that occur during exercise.

To determine if whole body glucose uptake increases as a linear function of $\dot{V}O_2$, a study was designed in which subjects would be examined at three different metabolic rates: 1) while resting, 2) during constant work rate low-intensity exercise (no increase in blood lactate), and 3) during high-intensity exercise (marked increase in blood lactate). Gas exchange was measured breath by breath, peripheral blood glucose turnover was assessed using the tracer 6,6-dideuteroglucose, and levels of epinephrine, norepinephrine, and insulin [immunoreactive insulin (IRI)] were measured in normal subjects at rest and at the high and low-intensity work rates. In this way, cardiorespiratory and metabolic responses to the same work rate input could be assessed simultaneously.

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 $\dot{V}O_2$ ($\dot{V}O_{2max}$ and $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ and the lactate or AT (41). The

FIG. 1. Breath-by-breath $\dot{V}O_2$ uptake ($\dot{V}O_2$) and heart rate (HR) during last 5 min of rest and 40 min of high-intensity [above anaerobic threshold (AT)] and low-intensity (below-AT) exercise. There were large increases in $\dot{V}O_2$ and HR for both types of exercise. High-intensity exercise was characterized by continuously increasing HR and $\dot{V}O_2$ despite constant work rate. Last several minutes of HR during high-intensity exercise were not recorded because of technical difficulties caused by sweat interfering with skin electrode.

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 $\dot{V}O_{2\max}$. These work rates were chosen so that low-intensity exercise would result in a significant and easily measurable increase in $\dot{V}O_2$ 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 $79 \pm 4\%$ $\dot{V}O_{2\max}$ 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-in-

tensity 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 $[6,6-^2H_2]$ glucose, and a constant infusion of the tracer was begun via catheterization of an antecubital vein. We chose $[6,6-^2H_2]$ 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 $0.079\text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Based on our previous studies of glucose turnover (11), we used the value of $3\text{ mg}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ 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 glucose was isolated using standard techniques. The aldonitrile pentacetate 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	$\dot{V}O_{2\max}$, l/min	AT, l/min	AT/ $\dot{V}O_{2\max}$, %	$\dot{V}O_{2\max}$ /kg, $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$	AT/kg,* $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$	Low-Intensity Work Rate, W	High-Intensity Work Rate, W	Low-Intensity $\dot{V}O_2$, % $\dot{V}O_{2\max}$	High-Intensity $\dot{V}O_2$, % $\dot{V}O_{2\max}$
1	24	84	4.25	2.05	48	51	24	65		32	
2	27	76	4.49	3.22	72	59	42	115		39	
3	23	65	3.53	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 $\pm$ SE	27 $\pm$ 1	76 $\pm$ 3	3.72 $\pm$ 0.24	2.35 $\pm$ 0.20	63 $\pm$ 3	50 $\pm$ 4	32 $\pm$ 3	87 $\pm$ 7	190 $\pm$ 10	40 $\pm$ 4	79 $\pm$ 4

* Anaerobic 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	High-intensity exercise	Rest	Low-intensity exercise	Rest	High-intensity exercise	Rest	Low-intensity exercise	Rest	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	0.40	2.53	0.28	0.99	0.30	2.23	51	90	64	148
4	0.35	1.41	0.40	3.05	0.32	1.33	0.37	3.02	62	102	59	162
5	0.27	1.11	0.41	2.45	0.23	1.01	0.32	2.28	67	98	58	128
6	0.47	1.74	0.35	2.28	0.31	1.47	0.31	2.30	74	114	76	178
7	0.34	1.54	0.48	3.10	0.22	1.36	0.36	3.15	77	116	83	171
Means	0.35±0.02	1.43±0.09*	0.41±0.02	2.68±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†
	±SE											

$\dot{V}O_2$, 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 $\pm$ 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 ($\dot{V}_E$, 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 $\dot{V}_E/\dot{V}O_2$ and end-tidal PO_2 increase without an increase in $\dot{V}_E/\dot{V}CO_2$ 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 $\pm$ 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

FIG. 3. Isotopic molar ratio, glucose production (R_a), and glucose uptake (R_d) during rest and high- and low-intensity exercise. Closed triangles, high-intensity protocol; open squares, low-intensity protocol. Data points, mean $\pm$ SE at each sampling interval. Molar ratio did not change during low-intensity exercise compared with resting values but decreased markedly with high-intensity protocol. This is reflected in the considerable increase in R_a and R_d during high-intensity exercise. There was virtually no change in R_a and R_d during low-intensity work.

both rest and low-intensity exercise (Table 2) (e.g., above-AT exercise caused an 8-fold increase over resting values).

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 signifi-

cantly higher during high-intensity exercise (mean 3.41 ± 0.66 mM, $P < 0.01$ compared with resting values).

We have quantified enrichment here as the molar ratio of $[6,6-^2\text{H}_2]\text{glucose}$ to total glucose (expressed as percent), which is similar to specific activity used in radioactive tracer studies. The mean values during rest and exercise for glucose concentration, molar isotopic ratio, R_a , and R_d of each subject are shown in Table 3. No changes were found in the mean glucose concentrations of the resting and exercise conditions, indicating homeostatic regulation of blood glucose. Although there was no change in mean molar isotopic enrichment between rest and low-intensity exercise, there was a significant reduction in enrichment during high-intensity exercise. Consequently, there was no difference between glucose turnover (R_a , R_d) during rest and low-intensity exercise. Only during high-intensity exercise was there a significant increase in glucose turnover above resting values. R_a did not differ from R_d under any of the conditions studied.

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 $\mu\text{U}/\text{ml}$) 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-

TABLE 3. Mean values of glucose concentration, molar isotopic ratio, glucose production, and glucose uptake

Subject	Rest	Low-Intensity Exercise	Rest	High-Intensity Exercise	Rest	Low-Intensity Exercise	Rest	High-Intensity Exercise
Glucose concentration, mg/100 mg					Molar isotopic ratio, %			
1	73.0	77.9			3.05	3.14		
2	90.0	90.4			1.83	1.86		
3	87.5	90.9	82.6	80.0	1.94	2.00	2.72	1.94
4	86.5	92.1	87.0	139.5	1.67	1.50	3.40	2.46
5	92.8	100.8	87.4	94.0	2.32	2.38	2.18	1.68
6	86.8	94.0	91.1	96.5	2.57	2.56	3.40	2.46
7	99.6	104.3	89.6	94.1	2.22	2.28	1.90	1.51
Means±SE	88.0±2.8	92.9±3.0	87.6±1.3	100.8±9.0	2.23±0.17	2.25±0.19	2.72±0.28	2.01±0.18*
R_a , mg·min ⁻¹ ·kg ⁻¹					R_d , mg·min ⁻¹ ·kg ⁻¹			
1	1.34	1.22			1.42	1.43		
2	3.99	4.20			4.40	3.85		
3	2.41	2.59	1.42	5.39	2.12	2.61	1.40	6.03
4	4.43	5.22	5.03	12.35	3.93	4.55	4.80	9.31
5	3.14	3.81	3.43	8.01	3.26	2.87	3.38	7.70
6	2.88	3.37	3.30	6.00	2.32	3.22	3.12	5.77
7	2.63	2.77	3.53	6.53	2.65	2.89	2.49	6.12
Means±SE	2.97±0.36	3.31±0.45	3.34±0.57	7.65±1.25*	2.87±0.39	3.06±0.37	3.03±0.56	6.98±0.67*

R_a , glucose production; R_d , glucose uptake. * Differed significantly from resting, $P < 0.05$.

tions). We found no statistically significant increase in mean R_a and R_d 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 $\dot{V}O_2$. 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 ($\dot{V}O_2$).

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 $\dot{V}O_{2\max}$. 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 R_a or R_d 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 those tissues (e.g., to adipose tissue or nonexercising muscle). As a result, R_a and R_d (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 (36–40% $\dot{V}O_{2\max}$) when leg blood flow and $\dot{V}O_2$ begin to account for most of the total body blood flow and $\dot{V}O_2$. The five subjects in our study who exercised at above lactate or anaerobic threshold work rates (79% $\dot{V}O_{2\max}$) represented the highest work intensity and highest value for whole body glucose uptake of the studies reviewed in which whole body glucose uptake was measured. Our data and the values obtained from the highest intensity exercise in Wahren's study appear to describe an almost

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 $\pm$ 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.

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. 5. Glucose uptake (mmol/min) during exercise as a function of metabolic rate ($\% \dot{V}O_{2 \max}$). 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 value for the 7 cited studies (closed circles) was the average of all 7 studies. Wahren et al. did not provide $\dot{V}O_{2 \max}$ 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 $\dot{V}O_{2 \max}$ (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 $\dot{V}O_{2 \max}$. Our data, in combination with those of Wahren, suggest an almost exponential increase in glucose uptake as metabolic rate approaches $\dot{V}O_{2 \max}$.

jects, increases in whole body glucose uptake may begin to reflect increases in the uptake of circulating blood glucose by the exercising leg muscles. However, for light to moderate exercise, the time dependent effects are most marked after 40 min of exercise. For example, Ahlborg and co-workers (1) demonstrated that during light exercise (30% of $\dot{V}O_{2 \max}$) arterial glucose concentrations began to fall only after 40 min. Moreover, they found that the largest amount of leg glucose uptake occurred at 90 min of exercise.

Sympathetic nervous system and adrenal responses as well as insulin play a role in maintaining blood glucose homeostasis during exercise, but there has been controversy as to the relative importance of these regulatory mechanisms (17, 27). Our data demonstrate that there is a substantial range of work rates in which exercise can be performed without an increase in peripheral glucose turnover. The results for glucose turnover were mirrored by the responses of catecholamines. During low-intensity exercise, the small changes in catecholamines were minor compared with those occurring in high-intensity exercise and were far smaller, proportionally, than changes in the $\dot{V}O_2$. 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_a and R_d , 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

TABLE 4. *Representative studies of glucose turnover during exercise in human subjects*

Year	Protocol Work Rate	$\dot{V}O_{2\max}$	AT or LT Measured	Constant or Work Rate	Simultaneous $\dot{V}O_2$ or HR Measurement	Tracer	Ref. No.
1980	50–60% $\dot{V}O_{2\max}$	Predicted*	No	Constant	$\dot{V}O_2$ and HR	[3- 3 H]glucose	28
1982	50% $\dot{V}O_{2\max}$	Predicted*	No	Constant	$\dot{V}O_2$ and HR	[3- 3 H]glucose	44
1982	60% $\dot{V}O_{2\max}$	Predicted*	No	Variable†	HR only	[3- 3 H]glucose	9
1984	40% $\dot{V}O_{2\max}$	Measured	No	Constant	Not stated	[3- 3 H]glucose	33
1985	60% $\dot{V}O_{2\max}$	Predicted*	No	Variable†	HR only	[3- 3 H]glucose	20
1986	55–60% $\dot{V}O_{2\max}$	Measured	No	Constant	$\dot{V}O_2$ and HR	[3- 3 H]glucose	16
1986	Above and below AT	Measured	Yes	Constant	$\dot{V}O_2$ and HR	[3- 3 H]glucose	11
1986	55% $\dot{V}O_{2\max}$	Predicted*	No	Variable†	HR only	[2- 3 H]glucose	21

$\dot{V}O_2$, O_2 uptake; $\dot{V}O_{2\max}$, maximal $\dot{V}O_2$; AT, anaerobic threshold; LT, lactate threshold; HR, heart rate. * Based on constant work rate submaximal measurements. † Adjusted to subject's HR.

intensity or glucose turnover.

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 “ O_2 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 mammalian muscle cells. More recently, Bylund-Fellenius et al. (7), using intramuscular PO_2 probes, demonstrated marked increases in muscle glucose uptake as tissue PO_2 fell 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 increased in exercising dogs when O_2 flow to the working muscles was reduced by anemia.

However, regardless of the underlying mechanism responsible 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 during 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 $\dot{V}O_{2\max}$. 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 $\dot{V}O_{2\max}$ in sedentary individuals 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 $\dot{V}O_{2\max}$ 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 $\dot{V}O_{2\max}$, which introduces substantial error in the assessment of the relative work intensity actually performed by the subjects. It is noteworthy that Åstrand and Rodahl (3), whose predictive nomograms for $\dot{V}O_{2\max}$ are most often used, stated that direct measurement of $\dot{V}O_{2\max}$ “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 continuously increasing and subjects were experiencing fatigue. The inability to achieve steady states for HR and $\dot{V}O_{2\max}$ is characteristic of high-intensity (above-AT) exercise (Fig. 1).

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 (R_d) to the metabolic rate ($\dot{V}O_2$). This is done by converting R_d and $\dot{V}O_2$ to equivalent moles of CO_2 . If it is assumed that all of the measured glucose uptake (R_d) were oxidized to CO_2 , then the ratio of R_d to $\dot{V}O_2$ represents the largest contribution that could possibly 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 exercise, peripheral blood glucose oxidation could account for a small proportion of $\dot{V}O_2$, 12 and 15%, respectively, reflecting the fact that the metabolic rate changes much more markedly than does R_d during exercise. Thus glucose 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 rates increase in intensity.

This work was supported by the Southern California Affiliate of the American Diabetes Association and by National Heart, Lung, and Blood Institute Grant R01-HL11907-17.

Address for reprint requests: D. M. Cooper, A-17 Annex, Harbor-UCLA Medical Center, 1000 West Carson St., Torrance, CA 90509.

Received 8 July 1988; accepted in final form 13 April 1989.

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

- muscle in intact man in the basal state. *J. Clin. Invest.* 35: 671-682, 1956.
3. ÅSTRAND, P.-O., AND K. RODAHL. *Textbook of Work Physiology: Physiological Bases of Exercise* (2nd ed.). New York: McGraw-Hill, 1977.
 4. BEAVER, W. L., N. LAMARRA, AND K. WASSERMAN. Breath-by-breath measurement of true alveolar gas exchange. *J. Appl. Physiol.* 51: 1662-1675, 1981.
 5. BIER, D. M., K. J. ARNOLD, W. R. SHERMAN, 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.
 6. BIER, D. M., R. D. 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 dideuteroglucose. *Diabetes* 26: 1016-1023, 1977.
 7. BYLUND-FELLENUS, 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.
 8. CASABURI, R., T. W. STORER, I. BEN-DOV, AND K. WASSERMAN. Effect of endurance training on possible determinants of $\dot{V}_{O_2}$ during heavy exercise. *J. Appl. Physiol.* 62: 199-207, 1987.
 9. CHISHOLM, D. J., A. B. JENKINS, D. E. JAMES, AND E. W. KRAEGER. The effect of hyperinsulinemia on glucose homeostasis during moderate exercise in man. *Diabetes* 31: 603-608, 1982.
 10. CLEMENT, D. L., AND J. T. SHEPHERD. Regulation of peripheral circulation during muscular exercise. *Prog. Cardiovasc. Dis.* 19: 23-31, 1976.
 11. COOPER, D. M., D. H. WASSERMAN, M. VRANIC, AND K. WASSERMAN. Glucose turnover in response to exercise during high- and low- $\dot{V}_{O_2}$ breathing in man. *Am. J. Physiol.* 251 (Endocrinol. Metab. 14): E209-E214, 1986.
 12. DAVIS, J. A., M. H. FRANK, B. J. WHIPP, AND K. WASSERMAN. Anaerobic threshold alterations caused by endurance training in middle-aged men. *J. Appl. Physiol.* 46: 1039-1046, 1979.
 13. DIXON, W. J., AND F. J. MASSEY. *Introduction to Statistical Analysis* (3rd ed.). New York: McGraw-Hill, 1969, p. 263-282.
 14. FELIG, P., AND J. WAHREN. Amino acid metabolism in exercising man. *J. Clin. Invest.* 50: 2703-2714, 1971.
 15. HERBERT, V., K. S. LAU, C. W. GOTTLIEB, AND S. BLEICHER. Coated charcoal immunoassay of insulin. *J. Clin. Endocrinol. Metab.* 25: 1375-1384, 1965.
 16. HOELZER, D. R., G. P. DALSKY, W. E. CLUTTER, S. D. SHAH, J. O. HOLLOSZY, AND P. E. CRYER. Glucoregulation during exercise: hypoglycemia is prevented by redundant glycoregulatory systems, sympathochromaffin activation, and changes in islet hormone secretion. *J. Clin. Invest.* 77: 212-221, 1985.
 17. HOELZER, 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.
 18. HOHORST, H. J. Lactate assay. In: *Methods of Enzymatic Analysis*, edited by H. U. Bergmeyer. New York: Academic, 1962, p. 266-270.
 19. IDSTROM, J.-P., V. H. SUBRAMANIAN, B. CHANCE, T. SCHERSTEN, AND A.-C. BYLUND-FELLENUS. Oxygen dependence of energy metabolism in contracting and recovering rat skeletal muscle. *Am. J. Physiol.* 248 (Heart Circ. Physiol. 17): H40-H48, 1985.
 20. JENKINS, A. B., D. J. CHISHOLM, D. E. JAMES, K. Y. HO, AND E. W. KRAEGER. Exercise-induced hepatic glucose output is precisely sensitive to the rate of systemic glucose supply. *Metabolism* 34: 431-436, 1985.
 21. JENKINS, A. B., S. M. FURLER, D. J. CHISHOLM, AND E. W. KRAEGER. 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.
 22. JORFELDT, L., AND J. WAHREN. Leg blood flow during exercise in man. *Clin. Sci. Lond.* 14: 459-468, 1971.
 23. KALHAN, S. A., D. M. BIER, S. M. SAVIN, AND P. A. J. ADAM. Estimation of glucose turnover and ^{13}C recycling in the human newborn by simultaneous $[1-^{13}\text{C}]\text{glucose}$ and $[6,6-^2\text{H}_2]\text{glucose}$ tracers. *J. Clin. Endocrinol. Metab.* 50: 456-460, 1980.
 24. KATZ, A., AND K. SAHLIN. Regulation of lactic acid production during exercise. *J. Appl. Physiol.* 65: 509-518, 1988.
 25. LEE, W.-N. P., J. S. WHITTING, A. L. FYMAT, AND H. G. BOETTERGER. A least squares approach to the quantitation of stable isotopes in mass spectrometry. *Biomed. Mass Spectrom.* 10: 641-645, 1983.
 26. MARGARIA, R., H. T. EDWARDS, AND D. B. DILL. The possible mechanisms of contracting and paying the oxygen debt and the role of lactic acid in muscular contraction. *Am. J. Physiol.* 106: 689-715, 1933.
 27. MARTIN, M. J., D. L. HORWITZ, M. NATTRASS, J. F. GRANGER, H. ROCHMAN, AND S. ASH. Effects of mild hyperinsulinemia on the metabolic response to exercise. *Metabolism* 30: 688-694, 1981.
 28. MINUK, H. L., A. K. HANNA, E. B. MARLISS, M. VRANIC, AND B. ZINMAN. Metabolic response to moderate exercise in obese man during prolonged fasting. *Am. J. Physiol.* 238 (Endocrinol. Metab. 1): E322-E329, 1980.
 29. PEULER, J. D., AND G. A. JOHNSON. Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine, and dopamine. *Life Sci.* 21: 625-636, 1977.
 30. RADZIUK, J., K. H. NORWICH, AND M. VRANIC. Experimental validation of measurements of glucose turnover in nonsteady state. *Am. J. Physiol.* 234 (Endocrinol. Metab. Gastrointest. Physiol. 3): E84-E93, 1978.
 31. RANDLE, P. J., AND G. H. SMITH. Regulation of glucose uptake by muscle. The effects of insulin, anaerobiosis and cell poisons on the uptake of glucose and release of potassium by isolated rat diaphragm. *Biochem. J.* 70: 490-500, 1958.
 32. REICHARD, G. A., B. ISSEKUTZ, P. KIMBEL, R. C. PUTNAM, N. J. HOCHHELLA, AND S. WEINHOUSE. Blood glucose metabolism in man during muscular work. *J. Appl. Physiol.* 16: 1001-1005, 1961.
 33. SIMONSON, D. C., V. KOIVISTO, R. S. SHERWIN, E. FERRANNINI, AND R. HENDLER. Adrenergic blockade alters glucose kinetics during exercise in insulin-dependent diabetics. *J. Clin. Invest.* 73: 1648-1658, 1984.
 34. SNEDECOR, G. W., AND W. G. COCHRAN. *Statistical Methods* (6th ed.). Ames: Iowa State Univ. Press, 1967, p. 317-321.
 35. STEELE, R. Influences of glucose loading and of injected insulin on hepatic glucose output. *Ann. NY Acad. Sci.* 82: 420-430, 1959.
 36. SZAFRANEK, J., C. D. PFAFFENBERGER, AND E. C. HORNING. Separation of aldoses and alditols using thermostable open tubular glass capillary columns. *Anal. Lett.* 6: 479-493, 1973.
 37. SZAFRANEK, J., C. D. PFAFFENBERGER, AND E. C. HORNING. The mass spectra of some per-o-acetylaldononitriles. *Carbohydr. Res.* 38: 97-105, 1974.
 38. WAHREN, J., P. FELIG, G. AHLBORG, AND L. JORFELDT. Glucose metabolism during leg exercise in man. *J. Clin. Invest.* 50: 2715-2725, 1971.
 39. WASSERMAN, D. H., H. L. A. LICKLEY, AND M. VRANIC. Effect of hematocrit reduction on hormonal and metabolic responses to exercise. *J. Appl. Physiol.* 58: 1257-1262, 1985.
 40. WASSERMAN, K., J. E. HANSEN, D. Y. SUE, AND B. J. WHIPP. *Principles of Exercise Testing and Interpretation*. Philadelphia, PA: Lea & Febiger, 1987, p. 1-269.
 41. WASSERMAN, K., AND B. J. WHIPP. Coupling of ventilation of pulmonary gas exchange during nonsteady-state work in men. *J. Appl. Physiol.* 54: 587-593, 1983.
 42. WASSERMAN, K., B. J. WHIPP, AND J. A. DAVIS. Respiratory physiology of exercise: metabolism, gas exchange, and ventilatory control. *Int. Rev. Physiol.* 23: 180-211, 1981.
 43. WASSERMAN, K., B. J. WHIPP, S. N. KOYAL, AND W. L. BEAVER. Anaerobic threshold and respiratory gas exchange during exercise. *J. Appl. Physiol.* 35: 236-243, 1973.
 44. ZINMAN, B., E. B. MARLISS, A. K. HANNA, H. L. MINUK, AND M. VRANIC. Exercise in diabetic man: glucose turnover and free insulin responses after glycemic normalization with intravenous insulin. *Can. J. Physiol. Pharmacol.* 60: 1236-1240, 1982.