Lactate and Glucose Exchange across the Forearm, Legs, and Splanchnic Bed during and after Prolonged Leg Exercise

GUNVOR AHLBORG and PHILIP FELIG, *Department of Clinical Physiology, Karolinska Institute, Sodersjukhuset, S-100 64 Stockholm, Sweden; Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06510*

ABSTRACT The net exchange of glucose and lactate across the leg and the splanchnic bed and the arterial-deep venous (A-DV) differences for these substrates in the forearm were determined in healthy subjects during 3–3.5 h of leg exercise (bicycle ergometer) at 58% maximum O_2 uptake and during a 40-min post-exercise recovery period.

Leg glucose uptake rose 16-fold during exercise and throughout the exercise period exceeded splanchnic glucose output. The latter reached a peak increment (3.5 times basal) at 90 min and fell by 60% during the third hour. As a result, blood glucose declined 40%, reaching frank hypoglycemia (blood glucose, <45 mg/dl) in 50% of subjects at 3.5 h.

Splanchnic lactate uptake rose progressively during exercise to values four times the basal rate at 3 h in association with a rise in arterial lactate to 1.5 mM. There was, however, no significant net output of lactate from the legs beyond 90 min of exercise. In contrast, the A-DV lactate difference in the forearm became progressively more negative throughout exercise, reaching values three times the basal level at 3.5 h. The rise in arterial lactate during exercise was proportional to the elevation in plasma epinephrine, which rose ninefold.

During recovery, splanchnic lactate uptake rose further to values six times the basal rate, whereas lactate output by the legs was no greater than in the basal state. The A-DV lactate difference in the forearm became even more negative than during exercise, reaching values four times basal. During exercise as well as recovery, forearm uptake of blood glucose could account for no more than 25–67% of forearm lactate release. Leg glucose uptake during recovery was threefold to fivefold higher than in the basal state in the face of plasma insulin concentrations that were 60% below basal and in association with a respiratory exchange ratio of 0.7.

We conclude that (*a*) during prolonged leg exercise at 58% maximum O_2 uptake an imbalance between splanchnic glucose production and leg glucose utilization results in a fall in blood glucose that may reach hypoglycemic levels in healthy subjects; (*b*) there is a marked increase in the uptake of lactate by the splanchnic bed that cannot be attributed to increased output of lactate from the exercising legs; (*c*) lactate is released by forearm muscle and, together with other relatively inactive muscle, may be an important source of the increased lactate turnover during and after prolonged leg exercise; (*d*) the increasingly negative A-DV lactate difference in the forearm cannot be accounted for by uptake of blood glucose, suggesting the breakdown of glycogen in forearm muscle during and after leg exercise; (*e*) increased glucose uptake by the legs in association with hypoinsulinemia during recovery suggests an increase in insulin sensitivity that permits glycogen repletion in previously exercising muscle in the absence of food ingestion; and (*f*) the evidence for increased lactate output in the forearm and augmented glucose uptake in the legs during recovery raises the possibility that after leg exercise glycogen stores are decreasing in muscle that was relatively inactive (e.g., that of the forearm) while increasing in the previously exercising leg muscles.

INTRODUCTION

The effect of intensive exercise (60% or more of maximum aerobic power [maximum O_2 uptake]) on lactate

Dr. Felig is an Established Investigator of the American Diabetes Association.

Received for publication 6 July 1981 and in revised form 4 September 1981.

metabolism has been well characterized. Such exercise results in increased production of lactate by exercising muscle (1), a rise in arterial lactate concentration (2, 3), and increased uptake of lactate by splanchnic tissues (4, 5) and resting muscle (6). Less information is available regarding lactate metabolism during mild to moderate exercise (<60% maximum O_2 uptake [$\dot{V}O_2max$])[1], which can be sustained for prolonged periods (1–3 h or more). With such exercise plasma lactate levels remain unchanged or increase by <1 mM (7, 8), yet splanchnic lactate uptake increases twofold to threefold (lactate constitutes the major gluconeogenic precursor available to the liver [7]). The source of the lactate taken up in increased amounts by splanchnic tissues during prolonged exercise has not been identified. Although the exercising muscle would be the expected site of lactate production, during intensive exercise net lactate output by contracting muscle is demonstrable for only the initial 10–30 min of work (5, 9, 10). The possible contribution of resting or relatively inactive muscle to lactate turnover during prolonged exercise has not been examined. Data also are unavailable regarding the net exchange of lactate and glucose across muscle in the recovery period after prolonged exercise. This is of interest inasmuch as during recovery after short-term exercise lactate is taken up by the previously exercising muscle (10), and direct use of lactate by muscle for glycogen replenishment has been suggested (11). Furthermore, biopsy studies after prolonged exhaustive exercise have shown replenishment of muscle glycogen during postexercise recovery even in the absence of food ingestion (12). Whether this can be ascribed to increased uptake of glucose, increased uptake of lactate, or both has not been established. The present study was undertaken to evaluate net exchange of lactate and glucose across the legs and forearm during prolonged (3–3.5 h) leg exercise and in the postexercise recovery period. Splanchnic exchange of these substrates and arterial levels of glucoregulatory hormones also were examined.

METHODS

Subjects. 20 healthy nonobese adult male subjects were studied in the postabsorptive state after a 12 to 14-h overnight fast. Data on age, height, weight, and maximum oxygen uptake are presented in Table I. For 3–4 d immediately before the exercise period the subjects were told not to participate in any competitive athletics and to ingest meals consisting of 200–300 g of carbohydrate per day. All subjects were informed of the nature, purpose, and possible risks involved in the study before giving their voluntary, written consent. The procedures employed in these studies have been reviewed and approved by the respective institutional ethical committees.

TABLE I
Age, Height, Weight, Maximum Oxygen Uptake, and Work Load during Prolonged Exercise

	Mean	SE	Range
Age, *yr*	26	0.7	20–31
Height, *cm*	182	1.4	169–187
Weight, *kg*	71	1.6	57–82
Maximum oxygen uptake, *liters/min*	3.8	0.13	2.6–4.8
Work load, *W*	130	4.9	90–170

Procedure. The subjects were studied at rest, during 3–3.5 h of upright continuous leg exercise on a cycle ergometer at a work load corresponding to 58% of their $\dot{V}O_2max$ (Table I), and during a 40-min postexercise recovery period. Arm activity was limited to lightly holding the cycle handle bars during the exercise period. In 10 subjects (who exercised for 3 h) a Cournand catheter (No. 8) was introduced percutaneously into a medial antecubital vein and advanced to a right-sided hepatic vein under fluoroscope control, and Teflon catheters were inserted percutaneously into both femoral veins, a femoral artery, and an antecubital vein. In another 10 subjects (who exercised for 3.5 h) Teflon catheters were inserted percutaneously into a deep forearm vein and either a femoral artery and both femoral veins (four subjects) or a brachial artery (six subjects). In both groups of subjects, observations were continued during a 40-min postexercise recovery period. Because the arterial concentrations of substrates and hormones and the leg exchange of glucose and lactate were not significantly different in the two groups of subjects, these data were combined.

Patency of the catheters was maintained by intermittent flushing with saline; the hepatic venous catheter was flushed with 1.5% sodium citrate solution, a total of <0.3 g being administered over the course of the study. Indocyanine green was infused intravenously at a constant rate for estimation of leg (13) and hepatic blood flow (14, 15).

Analyses. Glucose (16), lactate (17), and pyruvate (18) were analyzed in whole blood, and glycerol was analysed (19) in plasma by enzymatic techniques. Plasma insulin and glucagon were analyzed by radioimmunoassay (20, 21). Plasma catecholamines were determined by a radioenzymatic technique (22). Oxygen saturation was measured spectrophotometrically (23), and hemoglobin concentration was measured by the cyanmethemoglobin technique (24). The hematocrit was measured with a microcapillary hematocrit centrifuge and corrected for trapped plasma. Expired air was analyzed by the Scholander microtechnique (25). Data in the text and tables are given as mean±SE. Standard statistical methods have been employed; the paired *t* test was used when applicable (26).

RESULTS

Heart rate, pulmonary and splanchnic oxygen uptake, and blood flow (Table II). The heart rate rose to 140–150 beats/min during the exercise period and remained above basal value 40 min after exercise ($P < 0.001$). Pulmonary oxygen uptake rose more than sevenfold at 40 min of exercise ($P < 0.001$) and in-

[1] *Abbreviations used in this paper*: A-DV, arterial-deep venous; $\dot{V}O_2max$, maximum O_2 uptake.

TABLE II

*Heart Rate, Oxygen Uptake, and Regional Blood Flow during and after Prolonged Exercise**

		Exercise					Recovery		
	Rest	40 min	90 min	120 min	180 min	210 min	10 min	20 min	40 min
Heart rate, *beats/min*	52±2	141±5‡	148±5‡	148±5‡	157±6‡	150±4‡	96±1‡	94±3‡	85±4‡
Pulmonary oxygen uptake, *ml/min*	283±16	2,137±106‡	2,269±83‡	2,155±93‡	2,305±100‡	2,234±115‡	381±21§	353±25§	—
Respiratory exchange ratio	0.77±0.01	0.86±0.02‡	0.84±0.01‡	0.86±0.01‡	0.84±0.01‡	0.79±0.03	0.70±0.03‖	0.67±0.03‖	—
EHBF,¶ *liters/min*	1.37±0.17	0.76±0.05‖	0.65±0.05‖	0.63±0.05‖	0.68±0.09‖	—	1.08±0.07	1.09±0.06	1.38±0.06
A-HV oxygen difference,** *ml/liter*	40.4±3.5	123.3±9.3‡	148.9±8.4‡	156.6±10.2‡	135.5±4.8‡	—	87.8±5.9‖	94.6±6.7‖	87.7±5.7‖
Splanchnic oxygen uptake, *ml/min*	61±9	102±9‖	101±6‖	100±7‖	115±8‖	—	90±3‖	107±4‖	116±8‖
A-DV oxygen difference,‡‡ *ml/liter*	81.6±8.9	—	—	59.2±12.8	57.5±15.3	62.0±15.3	68.1±12.7	65.3±10.7	66.5±6.7
Deep vein oxygen saturation, %	54.9±3.6	—	—	66.3±5.5§	59.5±6.8	66.1±5.8§	66.8±4.8§	64.4±3.6§	63.2±3.5§
Leg blood flow, *liters/min* (two legs)	1.15±0.06	8.54±0.18‡	8.93±0.40‡	8.57±0.31‡	7.23±0.68‡	—	1.72±0.25§	1.41±0.18	1.30±0.10
A-FV oxygen difference,§§ *ml/liter*	60.0±4.4	158.6±4.1‡	160.7±3.4‡	161.7±4.6‡	159.2±2.1‡	—	52.4±1.9	61.9±5.5	55.8±2.3
Femoral vein oxygen saturation, %	70.9±2.1	—	—	29.1±1.0‡	27.4±1.8‡	—	77.5±2.0	74.8±3.3	78.2±1.7
Leg oxygen uptake, *ml/min*	68±4	1,353±40‡	1,432±54‡	1,381±36‡	1,450±96‡	—	90±13§	85±6§	72±4

* Data are given as mean±SE.

‡ Significantly different from resting value, $P < 0.001$.

§ Significantly different from resting value, $P < 0.05$.

‖ Significantly different from resting value, $P < 0.01$.

¶ EHBF, estimated hepatic blood flow.

** A-HV, arterial hepatic venous.

‡‡ A-DV, arterial deep venous (forearm).

§§ A-FV, arterial femoral venous.

creased further toward the end of exercise. The ventilatory exchange ratio rose during the first 40 min of exercise ($P < 0.001$) and subsequently fell after 2–3 h of exercise. During recovery there was a marked decline in the ventilatory exchange ratio to 0.67–0.70 ($P < 0.01$).

Leg blood flow rose approximately sevenfold from the resting value to 40 min of exercise and remained essentially unchanged during the rest of the exercise period. At cessation of work, leg blood flow fell, returning to the resting value after 20 min. Similarly, leg oxygen uptake increased ~20-fold during exercise and returned to the preexercise value within 40 min of recovery. Estimated hepatic blood flow fell by 45% at 40 min of exercise and showed a further 20% decrease up to 90 min of exercise ($P < 0.01$). Despite the fall in splanchnic blood flow, splanchnic oxygen uptake rose by ~70% at 40 min of exercise and thereafter was unchanged. The splanchnic oxygen uptake remained elevated above the basal value during the 40-min recovery period ($P < 0.01$). The deep (forearm) venous oxygen saturation rose during exercise and remained elevated during recovery ($P < 0.05$); the arterial deep venous oxygen difference in the forearm fell ($0.05 < P < 0.1$).

Arterial concentrations (Table III). The arterial concentration of glucose was unchanged up to 40 min of exercise and then fell, the most marked drop occurring during the third hour of exercise to a value 40% below basal ($P < 0.01$). After 3.5 h mean blood glucose fell to 2.56±0.13 mM. Blood glucose values fell to <2.5 mM in 50% of the 10 subjects who exercised for 3.5 h. 10 min after exercise the arterial glucose levels rose by ~20% ($P < 0.01$) but remained below base levels ($P < 0.01$) throughout the recovery period. Although the subjects were fatigued at the end of exercise, none complained of hunger, dizziness, or other symptoms attributable to hypoglycemia.

The arterial lactate level rose 0.50–0.60 mmol/liter during the first 2 h of exercise and increased by a further 0.5 mmol/liter between 2 and 3 h. The arterial lactate level declined after 10 min of recovery but remained 65% above basal value after the 40-min recovery period ($P < 0.01$). The pyruvate concentration showed a comparable pattern of change. The arterial glycerol level rose progressively during exercise, reaching a level more than 10 times basal ($P < 0.001$). After exercise glycerol fell gradually to a value three times the basal level 40 min after exercise ($P < 0.001$). The arterial free fatty acid concentration rose fourfold to fivefold by the end of exercise ($P < 0.001$). A further 25% increase occurred during the first 10 min of recovery ($P < 0.05$).

Arterial glucagon was unchanged at 40 min of exercise and then rose, reaching a value three times basal at 3 h of exercise ($P < 0.01$). During the 40-min recovery period the value remained elevated. Arterial insulin fell continuously during exercise ($P < 0.01$). The insulin level remained 40–50% below basal resting concentrations during recovery ($P < 0.01$).

The plasma epinephrine and norepinephrine concentrations rose ninefold during exercise ($P < 0.001$). After cessation of work the concentrations of both catecholamines fell but were still 2–2.5 times the basal values 40 min after exercise ($P < 0.01$). A direct linear correlation was observed between blood lactate and plasma epinephrine levels ($r = 0.54$, $P < 0.01$).

Splanchnic exchange (Table IV). Splanchnic glucose production rose during exercise to 3.5 the basal resting value at 90–120 min of exercise ($P < 0.001$) (Table V). During the third hour of exercise splanchnic glucose output fell by >50% ($P < 0.01$). A further reduction in splanchnic glucose output to the preexercise value was observed by 20 min of recovery.

Splanchnic uptake of glucose precursors increased during exercise (Table IV). Lactate uptake increased 2.5-fold for the first 120 min of exercise ($P < 0.01$). A further increase of 75% ($P < 0.01$) to four times the basal value was observed during the third hour of exercise. During recovery there was an additional increase in lactate uptake to a value five to six times the basal rate. The uptake of pyruvate and glycerol also increased during the last hour of exercise, reaching a value six times basal ($P < 0.01$), and increased further during the recovery period.

Leg exchange (Table IV). Leg glucose uptake increased 16-fold by 90 min of exercise ($P < 0.001$). During the last hour of exercise leg glucose uptake fell by 27% ($P < 0.001$). At cessation of work, leg glucose uptake fell but was still three to five times the basal value ($P < 0.001$) during recovery.

There was a significant net release of lactate by the leg in the resting state ($P < 0.01$). During exercise mean leg lactate production rose fourfold to sixfold up to 90 min of exercise ($P < 0.01$). However, after 120 and 180 min of exercise, no significant net output of lactate was observed. After exercise, leg lactate output returned to the basal value and remained unchanged over the 40-min recovery period. Leg pyruvate exchange followed the same pattern as lactate exchange. Leg glycerol output increased fourfold to sevenfold during exercise ($P < 0.01$). During the recovery period leg glycerol production showed an initial rise followed by a gradual decline, but remained five times the basal value 40 min after exercise ($P < 0.001$).

Forearm exchange (Table V). A significant net uptake of glucose across deep forearm tissues was observed in the basal state. The arterial-deep venous (A-DV) difference for glucose fell progressively during leg exercise, reaching a value 15% of the basal level

TABLE III

*Arterial Substrate and Hormone Concentrations during and after Prolonged Exercise**

		Exercise					Recovery		
	Rest	40 min	90 min	120 min	180 min	210 min	10 min	20 min	40 min
Glucose, *mmol/liter*	4.39±0.08	4.09±0.10	3.86±0.28‡	3.55±0.11§	2.78±0.13§	2.56±0.13§	3.12±0.13§	3.19±0.13§	3.18±0.10§
Lactate, *mmol/liter*	0.57±0.04	1.19±0.16§	1.31±0.29§	1.09±0.11§	1.56±0.16§	1.55±0.21§	1.50±0.15§	1.23±0.13§	0.94±0.10§
Pyruvate, *mmol/liter*	0.054±0.005	0.098±0.017§	0.094±0.020§	0.095±0.020§	0.141±0.023§	—	0.134±0.028§	0.118±0.025§	0.097±0.026§
Glycerol, *mmol/liter*	0.05±0.01	0.24±0.06‡	0.38±0.07‖	0.46±0.08‖	0.57±0.04‖	—	0.43±0.02‖	0.31±0.02‖	0.18±0.01‖
Free fatty acids, *mmol/liter*	0.43±0.09	0.66±0.16	0.83±0.11‖	1.11±0.14‖	1.92±0.18‖	—	2.47±0.21‖	2.23±0.13‖	1.72±0.06‖
Glucagon, *pg/ml*	77±8	66±13	111±15	158±36‡	257±53§	—	256±57§	222±44§	220±40§
Insulin, *μU/ml*	14.5±1.3	11.8±1.5	9.2±1.5§	8.0±1.6§	6.0±0.6§	—	8.3±1.5§	9.0±1.7§	7.5±1.2§
Epinephrine, *pg/ml*	75±27	262±55‖	—	627±135‖	754±164‖	1,026±163‖	421±102§	351±81§	283±62§
Norepinephrine, *pg/ml*	136±27	1,030±174‖	—	1,073±172‖	992±123‖	1,262±127‖	606±101§	442±85§	305±51§

* Mean±SE.

‡ Significantly different from resting value, $P < 0.05$.

§ Significantly different from resting value, $P < 0.01$.

‖ Significantly different from resting value, $P < 0.001$.

TABLE IV
*Splanchnic and Leg Exchange of Substrates during and after Prolonged Leg Exercise**

		Exercise				Recovery		
	Rest	40 min	90 min	120 min	180 min	10 min	20 min	40 min
Splanchnic exchange, *mmol/min*								
Glucose	−0.84±0.16	−2.43±0.31‡	−2.99±0.16‡	−2.92±0.17‡	−1.12±0.12	−1.08±0.14	−0.72±0.09	−0.84±0.19
Lactate	0.17±0.05	0.46±0.10§	0.44±0.10§	0.39±0.05§	0.68±0.13‡	0.96±0.27§	0.77±0.24¶	0.82±0.35¶
Pyruvate	0.010±0.013	0.016±0.013	0.028±0.008§	0.038±0.007§	0.062±0.007‡	0.083±0.016‡	0.066±0.009‡	0.077±0.030‡
Glycerol	0.05±0.02	0.14±0.05	0.20±0.06§	0.21±0.04§	0.33±0.03‡	0.40±0.02‡	0.29±0.02‡	0.21±0.01‡
Leg exchange,** *mmol/min*								
Glucose	0.22±0.03	2.64±0.35‡	3.59±0.31‡	3.40±0.30‡	2.48±0.25‡	1.06±0.12‡	0.91±0.14‡	0.66±0.07‡
Lactate	−0.13±0.02	−0.55±0.19§	−0.75±0.37§	−0.01±0.26	−0.06±0.32	−0.19±0.05	−0.18±0.08	−0.18±0.04
Pyruvate	0.009±0.003	−0.122±0.045§	−0.121±0.060§	−0.136±0.160	−0.014±0.046	−0.008±0.004	−0.014±0.010	−0.006±0.004
Glycerol	−0.03±0.01	−0.12±0.06§	−0.10±0.03§	−0.22±0.06§	−0.14±0.06§	−0.27±0.03‡	−0.22±0.01‡	−0.15±0.01‡

* Mean±SE.
‡ Significantly different from resting value, $P < 0.001$.
§ Significantly different from resting value, $P < 0.01$.
¶ Significantly different from resting value, $P < 0.05$.
** Both legs.

TABLE V

*A-DV Differences for Glucose and Lactate across Forearm during and after Prolonged Leg Exercise**

		Exercise						Recovery		
	Rest	40 min	120 min	180 min	190 min	200 min	210 min	10 min	20 min	40 min
A-DV, glucose, *mmol/liter*	0.42±0.07	0.22±0.03‡	0.08±0.03§	0.07±0.04§	0.11±0.03§	0.08±0.03§	0.05±0.02§	0.18±0.04‖	0.15±0.04‖	0.14±0.02‖
A-DV, lactate, *mmol/liter*	−0.15±0.04	−0.15±0.04	−0.24±0.04‡	−0.33±0.06‡	−0.37±0.03‖	−0.43±0.03‖	−0.40±0.03‖	−0.48±0.07‖	−0.57±0.11‖	−0.54±0.08‖

* Mean±SE.
‡ Significantly different from resting values, $P < 0.05$.
§ Significantly different from resting value, $P < 0.001$.
‖ Significantly different from resting value, $P < 0.01$.

at 3 h of exercise ($P < 0.001$). During recovery the A-DV difference for glucose rose threefold but remained below the basal value ($P < 0.01$).

A significant net release of lactate across the forearm was observed at rest ($P < 0.01$). The A-DV difference for lactate was unchanged during the first 40 min of exercise. However, as exercise continued beyond 40 min, this value became progressively more negative, reaching a value two to three times basal after 2–3.5 h of exercise ($P < 0.01$). During the recovery period the A-DV difference for lactate became even more negative than during exercise, reaching a value four times basal ($P < 0.01$).

DISCUSSION

The data presented above confirm and extend our previous observations with regard to leg uptake of glucose and splanchnic exchange of glucose and lactate during prolonged exercise (7) and demonstrate that these responses are exaggerated when the intensity of the exercise is increased. As in the case of leg exercise performed at 30% of $\dot{V}O_2$max for 4 h (7), leg exercise continued for 3–3.5 h at 58% of $\dot{V}O_2$max was associated with a marked increase in leg glucose uptake, which reached a peak at 90 min and was accompanied by a rise in splanchnic glucose output. However, with the more intensive exercise used in the present study, leg glucose uptake (Table III) was 20–60% greater than that observed with less intensive exercise (2.3–2.4 mmol/min [7]). Furthermore, blood glucose showed a decline in 3–3.5 h (1.83±0.15 mmol/liter) that was 30% greater than that observed after 4 h of lighter exercise (1.39±0.20) (7).

The development of frank hypoglycemia in healthy subjects during prolonged exercise has previously been reported, primarily in marathon runners (27, 28). The current data reveal that when exercise is maintained at 58% of $\dot{V}O_2$max for 3.5 h, blood glucose levels fall below 2.5 mM in 50% of subjects. The hypoglycemia can be accounted for by the fact that throughout exercise splanchnic glucose output was consistently lower than leg glucose uptake (Table IV). Furthermore, the period of most rapid decline in blood glucose (120–180 min) was associated with the most marked decline in splanchnic glucose output (Table IV). In keeping with the greater decline in blood glucose found in the present investigation as compared with our earlier study with less intensive exercise (7), splanchnic glucose production at 3 h (1.12±0.12 mmol/min) was 40% lower than that observed after 3 h of less intensive exercise (1.92±0.36 mmol/min) (7).

Total estimated splanchnic glucose release during exercise calculated on the basis of linear interpolations between the individual measurements amounted to 75 g after 3 h of exercise. This value is the same as the estimated total splanchnic glucose output observed after 4 h of exercise at 30% $\dot{V}O_2$max (7). Since the total amount of glycogen content in the liver in healthy postabsorptive man has been reported to be 75–90 g (29), a considerable amount of liver glycogen must have been mobilized during the exercise period. This is also suggested by the marked fall in splanchnic glucose output during the third hour of exercise and the accompanying fall in arterial glucose levels.

Despite the fall in splanchnic glucose output, the uptake of glucose precursors (lactate, pyruvate, glycerol) increased during exercise, so that by the third hour their uptake (if converted to glucose) could account for ~60% of total splanchnic glucose output. Lactate uptake and pyruvate uptake by the splanchnic bed after 3 h of exercise at 58% $\dot{V}O_2$max (Table IV) were, respectively, 80 and 200% greater than that observed after 3 h of exercise at 30% $\dot{V}O_2$max (0.38±0.06 and 0.02±0.010 mmol/min, respectively) (7), but virtually identical to the values observed after 4 h of the less intensive exercise (0.65±0.07 and 0.057±0.016 mmol/min, respectively) (7). Thus, with respect to the

fall in blood glucose, the imbalance between splanchnic glucose output and leg glucose uptake and the rise in splanchnic uptake of gluconeogenic precursors, which have been shown to characterize prolonged (3 h or more) exercise (7), the present data demonstrate that these responses are accelerated and exaggerated when the intensity of the exercise is increased from 30 to 58% $\dot{V}O_2$max.

The current findings are of particular interest with respect to the data regarding leg and arm exchange of lactate during prolonged leg exercise as well as the data on splanchnic and peripheral substrate exchange during the postexercise recovery period. A net release of lactate from the exercising legs was observed only for the first 90 min. At 120 and 180 min no significant leg output of lactate was demonstrable (Table IV). Nevertheless, arterial lactate levels and splanchnic uptake of lactate rose 40 and 75%, respectively, between 120 and 180 min. (Tables III and IV). These observations clearly indicate that during prolonged leg exercise production of lactate is increasing at some site other than the exercising legs.

The data on the A-DV differences for lactate across the forearm indicate a possible site of lactate production. During prolonged leg exercise the A-DV difference for lactate across the forearm became progressively more negative. Such a change in A-DV difference cannot be equated with an increase in net lactate release in the absence of data on blood flow. Although blood flow was not measured, oxygen saturation in the deep forearm vein rose during exercise (Table II), suggesting that blood flow did not decline and may have increased. Studies performed during single leg exercise have shown a threefold increase in blood flow in the inactive leg (6). The data thus suggest that forearm muscle is a site of increased lactate release and contributes to the augmented delivery of lactate to the splanchnic bed during prolonged leg exercise.

It should be noted that during upright leg exercise on the cycle ergometer, some contraction of arm muscle is taking place, because the subjects are holding the handlebars. The extent of such contraction is, of course, far less than that occurring in the legs, and thus may be considered representative of "resting" (relatively inactive) muscle during leg exercise. In nonobese subjects total muscle mass is estimated to be 40% of body weight (30); leg muscle amounts to ~50% of total muscle. The total mass of "resting" muscle during leg exercise thus is ~14 kg. Assuming that blood flow to muscle in the resting state is 30 ml/kg per min (31), and that blood flow to relatively inactive muscle increases threefold during leg exercise (6), lactate production by "resting" muscle after 3–3.5 h of leg exercise may be estimated at 0.4–0.5 mmol/min. This output of lactate from relatively inactive muscle could account for 60–70% of splanchnic lactate utilization after 3–3.5 h of leg exercise (Table IV).

The importance of tissues other than the leg as sites of increased lactate production is also evident in the recovery period after prolonged leg exercise. During the initial 10 min of recovery splanchnic lactate uptake rose 50% in the absence of a significant fall in arterial lactate. Furthermore, net release of lactate from the legs throughout recovery was not significantly greater than that in the basal state, yet splanchnic lactate uptake was five to six times the preexercise level. It is of interest in this regard that the A-DV lactate difference in the forearm increased by 20–40% in the recovery period, reaching values threefold to fourfold greater than those of the preexercise resting state. Because it is highly unlikely that forearm blood flow in the postexercise recovery period is reduced 67–75% from the preexercise basal value, our findings suggest that the stimulatory effect of prolonged leg exercise on lactate production by forearm muscle persists in the recovery phase after leg exercise.

A comparison of the A-DV lactate and glucose differences provides some insight into the relative importance of blood-borne glucose vs. *in situ* muscle glycogen breakdown in the formation of lactate by forearm muscle. Recognizing that each mole of glucose taken up by muscle can contribute two moles of lactate, blood glucose uptake (if completely converted to lactate) can account for no more than 20–67% of forearm lactate output after 2–3.5 h of exercise (Table V). Similarly, in the recovery period blood glucose uptake can account for at most 25–67% of forearm lactate release (Table V). These data thus suggest that the release of lactate from forearm muscle during and after prolonged leg exercise is due, at least in part, to breakdown of glycogen stores in muscle forearm.

The current findings of lactate release from relatively inactive forearm muscle during leg exercise contrast with earlier observations on the metabolism of inactive muscle during single leg exercise (6, 32) or arm exercise (6). In those studies the exercise of one leg was associated with lactate uptake in the inactive leg (6, 32). Similarly, during arm exercise the legs showed a net uptake of lactate (6). It should be noted however, that the exercise in those studies was only for 20–40 min and was accompanied by arterial blood lactate levels (3.8–4.4 mmol/liter) that were twofold to threefold greater than those in the present study (6). Thus, whether relatively inactive muscle becomes a site of lactate use or production during exercise may depend on the duration of the exercise and the ambient arterial lactate levels. With brief exercise resulting in a sixfold to eightfold increase in arterial lactate, "resting" muscle is a site of lactate use. In contrast, with exercise lasting 2 h or more and causing only a twofold

to threefold increase in arterial lactate, "resting" muscle is a site of lactate production.

With respect to the mechanism of these changes in lactate, and presumably glycogen metabolism in forearm muscle during and after prolonged leg exercise, the rise in plasma catecholamines may be of some importance. A significant correlation between plasma epinephrine and blood lactate levels was observed. Furthermore, the plasma catecholamine levels remained significantly elevated above basal values in the recovery period. Thus, in addition to the direct effects of the contractions which occur to some extent in relatively inactive muscles during leg exercise (6), the rise in catecholamines may constitute a stimulus to glycogen breakdown and lactate production in forearm. The failure to observe ongoing lactate release from the exercising legs (i.e., beyond 90 min), despite the sustained elevations in plasma catecholamines, may reflect the progressive depletion of the glycogen content of active muscle that accompanies prolonged exercise of moderate intensity (33).

In an earlier study of substrate metabolism during the recovery period after relatively brief (40 min) exercise, a rise in glucose uptake by the previously exercising legs was observed (10). The rise in glucose uptake after short-term exercise was associated with a rapid increase in arterial insulin to values two to three times the basal level (10). In the present study glucose uptake by the legs in the recovery period was threefold to fivefold greater than in the preexercise resting state. However, this increase occurred in the face of plasma insulin levels that were 40–50% below basal concentrations. These findings suggest that during the recovery phase after prolonged exercise there is an increase in insulin sensitivity in previously exercising muscle. These observations may thus provide an explanation for the partial replenishment of muscle glycogen that occurs after prolonged exercise, even in the absence of food intake (12). The findings are also in keeping with in vitro evidence of enhanced insulin sensitivity in perfused hindquarters obtained from rats immediately after treadmill exercise (34). Whether such an increase in insulin sensitivity is due to receptor or postreceptor-mediated changes remains to be established.

The data obtained in the recovery period with respect to leg lactate metabolism also differ from the observations after short-term exercise (10). After short-term (40 min) leg exercise a net uptake of lactate by the leg is observed over the first 20 min of recovery (10). In contrast, during recovery from prolonged leg exercise, there is a net output of lactate from the legs that is comparable to that observed in the basal state (Table IV). These differences during recovery may be a consequence not only of the difference in duration of exercise but may also be related to the higher arterial lactate levels (>2 mM) present at the onset of the recovery phase after short-term exercise (10).

The overall changes in glucose and lactate metabolism observed in the legs, forearm, and splanchnic bed during recovery raise the possibility of a redistribution of muscle glycogen stores after prolonged exercise. During recovery, the previously exercising legs are taking up glucose at a rate three to five times the basal rate in association with a respiratory exchange ratio of 0.7, suggesting that glucose is not being oxidized but is used for glycogen replenishment. In contrast, the previously "resting" forearm is releasing lactate at rates in excess of glucose uptake, suggesting muscle glycogen breakdown. The simultaneous increase in splanchnic uptake of lactate and the operation of the Cori cycle (glucose formation from lactate) provides a link between the changes in forearm and leg metabolism. In this manner there may, in effect, be a redistribution of glycogen during recovery from muscle that was relatively inactive (e.g., forearm) to the previously exercising leg muscles. Furthermore, the Cori cycle, which for >50 years has been known to involve the transfer of lactate from exercising muscle to liver for glucose production (35, 36), thus may also involve participation by relatively inactive muscle during and after prolonged leg exercise.

ACKNOWLEDGMENTS

This work was supported, in part, by grants from the National Institutes of Health (AM13526), the Kroc Foundation, Swedish Sports Federation (21-75 and 24-81), and the Swedish Medical Research Council—Karolinska Institute.

REFERENCES

1. Karlsson, J., and B. Saltin. 1970. Lactate, ATP, and CP in working muscle during exhaustive exercise in man. *J. Appl. Physiol.* **29:** 598–602.
2. Jervell, O. 1928. Investigation of the concentration of lactic acid in blood and urine. *Acta Med. Scand.* **24:** 1–135.
3. Bang, O. 1936. The lactate content of the blood during and after muscular exercise in man. *Scand. Arch. Physiol.* **177:** 455–462.
4. Rowell, L. B., G. L. Brengelmann, J. R. Blackman, R. D. Twiss, and F. Kusumi. 1966. Splanchnic removal of lactate and pyruvate during prolonged exercise in man. *J. Appl. Physiol.* **21:** 1773–1783.
5. Wahren, J., P. Felig, G. Ahlborg, and L. Jorfeldt. Glucose metabolism during leg exercise in man. *J. Clin. Invest.* **50:** 2715–2725.
6. Ahlborg, G., L. Hagenfeldt, and J. Wahren. 1975. Substrate utilization by the inactive leg during one-leg or arm exercise. *J. Appl. Physiol.* **35:** 718–723.
7. Ahlborg, G., P. Felig, L. Hagenfeldt, R. Hendler, and J. Wahren. 1974. Substrate turnover during prolonged exercise in man. Splanchnic and leg metabolism of glucose, free fatty acids, and amino acids. *J. Clin. Invest.* **53:** 1080–1090.
8. Jones, N. L., G. J. F. Heigenhauser, A. Kuksis, C. G.

Matsos, J. R. Sutton, and C. J. Toews. 1980. Fat metabolism in heavy exercise. *Clin Sci. (Oxf.).* **59:** 469–478.
9. Wahren, J. 1977. Glucose turnover during exercise in man. *Ann. N. Y. Acad. Sci.* **301:** 45–55.
10. Wahren, J., P. Felig, R. Hendler, and G. Ahlborg. 1973. Glucose and amino acid metabolism during recovery after exercise. *J. Appl. Physiol.* **34:** 838–845.
11. Hermansen, L. 1977. Lactate disappearance and glycogen synthesis in human muscle after maximal exercise. *Am. J. Physiol.* **233:** E422–E429.
12. Maehlum, S., and L. Hermansen. 1978. Muscle glycogen concentration during recovery after prolonged severe exercise in fasting subjects. *Scand. J. Lab. Clin. Invest.* **38:** 557–560.
13. Jorfeldt, L., and J. Wahren. 1971. Leg blood flow during exercise in man. *Clin. Sci. (Oxf.).* **41:** 459–473.
14. Bradley, S. E. 1948. Measurements of hepatic blood flow. *Methods Med. Res.* **1:** 199–204.
15. Rowell, L. B., J. R. Blackmon, and R. A. Bruce. 1964. Indocyanine green clearance and estimated hepatic blood flow during mild to maximal exercise in upright man. *J. Clin. Invest.* **43:** 1677–1690.
16. Huggett, A. S. G., and D. A. Nixon. 1957. Use of glucose oxidase, peroxidase and *o*-dianisidine in determination of blood and urinary glucose. *Lancet.* **II:** 368–370.
17. Wahren, J. 1966. Quantitative aspects of blood flow and oxygen uptake in the human forearm during rhythmic exercise. *Acta Physiol. Scand.* **67**(Suppl. 269): 1–92.
18. Bucher, T., R. Czok, W. Lamplrecht, and E. Latzko. 1962. Pyruvate. *In* Methoden der enzymatischen Analyse. H. U. Bergmeyer, editor. Verlag-Chemie, Weinheim/Bergstrasse, West Germany. 253–259.
19. Wieland, O. 1962. Glycerin. *In* Methoden der enzymatischen Analyse. H. U. Bergmeyer, editor. Verlag-Chemie, Weinheim/Bergstrasse, West Germany. 211–214.
20. Rosselin, G., R. Assan, R. A. Yalow, and S. A. Berson. 1966. Separation of antibody-bound and unbound peptide hormones labelled with iodine-131 by talcum powder and precipitated silica. *Nature (Lond.).* **212:** 355–357.
21. Aguilar-Parada, E., A. M. Eisentraut, and R. H. Unger. 1969. Pancreatic glucagon secretion in normal and diabetic subjects. *Am. J. Med. Sci.* **257:** 415–419.
22. Cryer, P. E. 1976. Isotope-derivative measurements of plasma norepinephrine and epinephrine in man. *Diabetes.* **25:** 1071–1082.
23. Drabkin, D. L. 1950. Measurement of O_2-saturation of blood by direct spectrophotometric determination. *Methods Med. Res.* **2:** 159–162.
24. Drabkin, D. L., and J. H. Austin. 1935. Spectrophotometric studies. II. Preparations from washed blood cells; nitric oxide hemoglobin and sulfhemoglobin. *J. Biol. Chem.* **112:** 51–65.
25. Scholander, P. F. 1947. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. *J. Biol. Chem.* **167:** 235–240.
26. Snedecor, G. W., and W. G. Cochran. 1967. Statistical Methods, 6th ed., Iowa State University Press, Ames.
27. Levine, S. A., G. Gordon, and C. L. Derick. 1924. Some changes in the chemical constituents of the blood following a marathon race. *J. Am. Med. Assoc.* **82:** 1778–1779.
28. Sutton, J., M. J. Coleman, A. P. Millar, L. Lazarus, and P. Russo. 1972. The medical problems of mass participation in athletic competition. The "city to surf" race. *Med. J. Aust.* **2:** 127–133.
29. Hultman, E., and L. H. Nilsson. 1971. Liver glycogen in man. Effect of different diets and muscular exercise. *In* Muscle Metabolism during Exercise. B. Pernow and B. Saltin, editors. Plenum Press, New York. 143–151.
30. Moore, F. D., K. H. Olesen, J. D. McMurrey, H. V. Parker, M. R. Ball, and C. M. Boyden. 1963. The body cell mass and its supporting environment. W. B. Saunders Company, Philadelphia. 58–173.
31. Bancroft, H. 1963. Circulation in skeletal muscle. *Hand. Physiol.* **2:** 1353–1385.
32. Freyschuss, V., and T. Strandell. 1968. Circulatory adaptation to one and two leg exercise in supine position. *J. Appl. Physiol.* **25:** 511–515.
33. Saltin, B., and J. Karlsson. 1971. Muscle glycogen utilization during work of different intensities. *In* Muscle Metabolism during Exercise. B. Pernow and B. Saltin, editors. Plenum Press, New York. 289–299.
34. Garetto, L. D., E. A. Richter, and N. B. Ruderman. 1981. Increased insulin sensitivity of skeletal muscle following exercise. *Diabetes.* **30**(Suppl. 1): 63A.
35. Cori, C. F., and G. R. Cori. 1929. Glycogen formation in the liver from *d*- and *l*-lactic acid. *J. Biol. Chem.* **81:** 389–401.
36. Himwich, H. E., Y. D. Koskoff, and L. H. Nahum. 1930. Studies in carbohydrate metabolism. I. A glucose-lactic acid cycle involving muscle and liver. *J. Biol. Chem.* **85:** 571–584.