

Systemic lactate kinetics during graded exercise in man

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STANLEY, WILLIAM C., EDWARD W. GERTZ, JUDITH A. WISNESKI, D. LYNN MORRIS, RICHARD A. NEESE, AND GEORGE A. BROOKS. *Systemic lactate kinetics during graded exercise in man*. Am. J. Physiol. 249 (Endocrinol. Metab. 12): E595–E602, 1985.—To investigate the relationships between oxygen consumption ($\dot{V}O_2$) and the rates of systemic lactate appearance (R_a) and disappearance (R_d), six healthy males were studied at rest and during continuous graded exercise using a primed continuous infusion of lactate tracer. Subjects exercised for 6 min at 300, 600, 900, and 1,200 kg·m·min⁻¹. L-(+)-[1-¹⁴C]lactate was infused intravenously, and arterial samples were drawn at rest and every 2 min throughout the exercise period. R_a and R_d were calculated using nonsteady-state equations. At rest R_a and R_d were 14.4 ± 1.8 and 15.1 ± 2.2 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively. Near steady-state values were observed toward the end of the first two work loads. R_a and R_d values were 32.8 ± 2.3 and 37.4 ± 1.3 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ during *min 5* and *6* at 300 kg·m·min⁻¹ and were 59.1 ± 2.6 and 55.4 ± 2.3 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ during *min 5* and *6* at 600 kg·m·min⁻¹. R_a was significantly greater than R_d at both 900 and 1,200 kg·m·min⁻¹. R_a and R_d averaged 145.4 ± 10.5 and 110.2 ± 5.6 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively, during the last 2 min at 900 kg·m·min⁻¹, and 309.4 ± 20.8 and 169.7 ± 10.6 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively, at 1,200 kg·m·min⁻¹. All subjects showed a linear relationship between R_a and lactate concentration and a curvilinear relationship between R_d and arterial lactate. R_a and R_d were both exponentially related to $\dot{V}O_2$. The metabolic clearance rate was significantly elevated above resting values during the first three exercise states (20.6 ± 1.6 ml·kg⁻¹·min⁻¹ at rest vs. 34.4 ± 2.5 ml·kg⁻¹·min⁻¹ at 600 kg·m·min⁻¹), then decreased to near resting values at 1,200 kg·m·min⁻¹. We conclude that during continuous graded exercise the lactate R_a and R_d increase exponentially with work load and that the R_a and R_d increase proportionately with arterial lactate concentration. The circulating lactate concentration increases during a graded exercise test because R_a increases more rapidly than R_d .

tracer methodology; substrate turnover; exercise metabolism; exertion

THE KINETICS OF LACTATE METABOLISM during exercise have generally been inferred from measurements of lactate concentration in blood and muscle. These measurements yield valuable, yet incomplete data on lactate metabolism. Through the infusion of isotopically labeled lactate, the turnover and oxidation rates of lactate can be determined. Lactate metabolism during steady state exercise has been studied in dogs (6, 8, 16, 17) and rats (7) using isotopic tracer techniques. Lactate turnover

and oxidation rates increase markedly from rest to moderate exercise with only a moderate increase in circulating lactate concentration (6, 7, 8, 16, 17).

During graded exercise, lactate concentration increases only slightly above resting values during the lower work loads. Lactate concentration increases sharply at a particular work load, which usually elicits between 50 and 80% of maximum oxygen consumption ($\dot{V}O_{2\text{max}}$) (15). The purpose of the present study was to investigate the kinetics of blood lactate in man during graded exercise to near $\dot{V}O_{2\text{max}}$ using a primed continuous infusion of isotopic lactate tracer. Our results demonstrate that the rates of lactate appearance and disappearance are exponential functions of oxygen consumption and are linearly related to arterial lactate concentration during graded exercise.

METHODS

Subjects. Six healthy male volunteers participated in the study (Table 1). Each subject underwent a complete medical history, physical examination, and laboratory tests. The laboratory tests included an electrocardiogram, chest X ray, complete blood count, liver function test, fasting glucose, blood urea nitrogen, creatinine, and urinalysis. All subjects were physically active: two were competitive long distance runners, two were recreational runners, one was a competitive cyclist, and one was a recreational swimmer. The protocols were approved by the Human Research Committee of the University of California, San Francisco, and the San Francisco Veterans Administration Medical Center. Each subject was informed of the nature of the study and written consent was obtained.

Protocol. Subjects were studied in the morning after a 12-h fast and a 36-h period without exercise. For isotope infusion a Teflon catheter was inserted into an antecubital vein of the left arm. A short polyethylene sheath was inserted into the brachial artery by the Seldinger technique for arterial blood samples.

Isotopically labeled lactate was administered using the primed-continuous infusion method. The L-(+)-[1-¹⁴C]-lactate (55 mCi/mM) was obtained from New England Nuclear. It was sterilized by Millipore filtration and diluted in 0.9% NaCl to a concentration of 10 $\mu\text{Ci}/\text{ml}$ for bolus injection and 0.3 $\mu\text{Ci}/\text{ml}$ for the subsequent constant infusion. After a priming bolus of 10 μCi ,

TABLE 1. Description of subjects

Subject	Weight, kg	Age	Activity	Peak $\dot{V}O_2$, ml·kg ⁻¹ ·min ⁻¹	Peak Lactate, mmol
1	65.8	21	Competitive runner	44.3	5.73
2	63.0	30	Competitive cyclist	48.1	9.35
3	74.8	19	Recreational runner	46.1	6.26
4	81.6	26	Recreational swimmer	45.0	11.29
5	64.9	22	Competitive runner	59.3	11.70
6	75.5	25	Recreational runner	44.9	10.14
Means	70.9	23.8		48.0	9.08
±SE	3.0	1.6		2.3	1.0

$\dot{V}O_2$, O_2 consumption.

[1-¹⁴C]lactate was infused at a constant rate of 10 μ Ci/h. The total dose approximated 23 μ Ci. It has previously been determined that steady-state lactate specific activities are achieved in resting humans after 20 min of infusion (11, 31). After 40 min of infusion at rest, a blood sample was drawn. Four minutes later another sample was drawn, then exercise began the following minute.

Subjects performed a continuous graded exercise test in the supine position on a cycle ergometer (Quinton Instruments Uniwork Ergometer). The work loads were 300, 600, 900, and 1,200 kg·m·min⁻¹ and each stage was 6 min in duration. A pedaling frequency of 60 rpm was maintained. To prevent the subject from sliding away from the ergometer while pedaling, a nylon rock climbing belt was securely fastened around the subject's waist and secured to the end of the catheterization table. Minute ventilation ($\dot{V}E$), $\dot{V}O_2$, and carbon dioxide output ($\dot{V}CO_2$) were measured during the last 10 min at rest and continuously during the exercise test using a Medical Graphics, System 2000.

During exercise, arterial blood samples were drawn during min 2, 4, and 6 of each work load. The exact time of each sampling was recorded for use in the calculation of the rates of blood lactate appearance (R_a) and disappearance (R_d). Subjects were encouraged to work for as long as possible.

Chemical analysis. Blood samples were immediately mixed with cold 7% perchloric acid (1:2 vol/vol) and centrifuged; the supernatant fluid was taken for future analysis. Lactate concentration was determined by an enzymatic spectrophotometric method (9). Lactate was separated by ion exchange chromatography by previously published methods (11). The protein-free fluid was neutralized and passed successively through Dowex-50 and Dowex-1 to remove labeled ionized compounds. Portions of the eluates containing lactate in 0.25 M sodium acetate were assayed by enzymatic methods. Other portions were mixed with Aquasol and ¹⁴C was determined by liquid scintillation counting. The specific activity was expressed in disintegration per minute per micromole.

Calculations. The R_a in and R_d from the lactate space

were calculated using the nonsteady-state equations of Steele (33)

$$R_a = [F - (V \times \overline{LA} \times \Delta SA / \Delta t)] / \overline{SA} \quad (1)$$

$$R_d = R_a - (V \times \Delta LA / \Delta t) \quad (2)$$

Where F is the infusion rate (dpm·kg⁻¹·min⁻¹), V is the lactate space or the volume of distribution, LA is the arterial lactate concentration (μ mol/ml), \overline{LA} is the mean concentration of the consecutive samples, SA is the specific activity of arterial lactate (dpm/ μ mol), and Δt is the time in minutes between the two samples.

Both R_a and R_d were expressed per unit body mass (μ mol·kg⁻¹·min⁻¹). The metabolic clearance rate (MCR), expressed in ml·kg⁻¹·min⁻¹, was calculated as

$$MCR = R_d / LA \quad (3)$$

Under non-steady conditions the calculation of lactate R_a and R_d require knowledge of the operation volume of distribution (V) in which the measured changes in lactate concentration and specific activity occur. To test the effects of large differences in the estimate of V, R_a , and R_d were calculated using a range of V (100–400 ml/kg). We selected a V of 100 ml/kg for the presentation of calculated results (see DISCUSSION).

Statistical methods. The difference between lactate concentration, R_a , R_d , and MCR at different time points and between R_a and R_d for a given time interval were determined using two-way analysis of variance. Comparisons between samples were made using the Students Newman-Keuls multiple range test. A difference of $P < 0.05$ between means was accepted as significant. Values for R_a and R_d at rest and during 3–4 and 5–6 min of each stage of exercise were used in the correlation of R_a and R_d with mean arterial lactate concentration and $\dot{V}O_2$ during the same period. Linear regression analysis was performed to describe the relationships between these parameters. Results are presented as mean \pm the SE of the mean.

RESULTS

Physical performance and respiratory gas exchange. All subjects advanced to 1,200 kg·m·min⁻¹. Three subjects (2, 5, and 6) completed 6 min at this stage and the remaining 3 subjects (1, 3, and 4) stopped after 4 min. Steady rate values for respiratory gas exchange were attained after the 1st min at 300 and 600 kg·m·min⁻¹ (Fig. 1). Pulmonary $\dot{V}E$ did not level off during exercise at 900 and 1,200 kg·m·min⁻¹, while $\dot{V}O_2$ and $\dot{V}CO_2$ did at 900 but not at 1,200 kg·m·min⁻¹. Peak $\dot{V}O_2$ occurred during the last minute of exercise and averaged 48.0 \pm 5.2 ml·kg⁻¹·min⁻¹ (Table 1).

Lactate concentration. Arterial lactate concentration at rest averaged 0.72 \pm 0.09 mM (Fig. 2). Arterial lactate concentration was slightly above resting values during the first two work loads (300 and 600 kg·m·min⁻¹). At 900 kg·m·min⁻¹, the lactate concentration increased significantly above the resting values and the values during the first two work loads. Peak lactate concentration during exercise occurred in the final sample and was 9.1 \pm 1.0 mM.

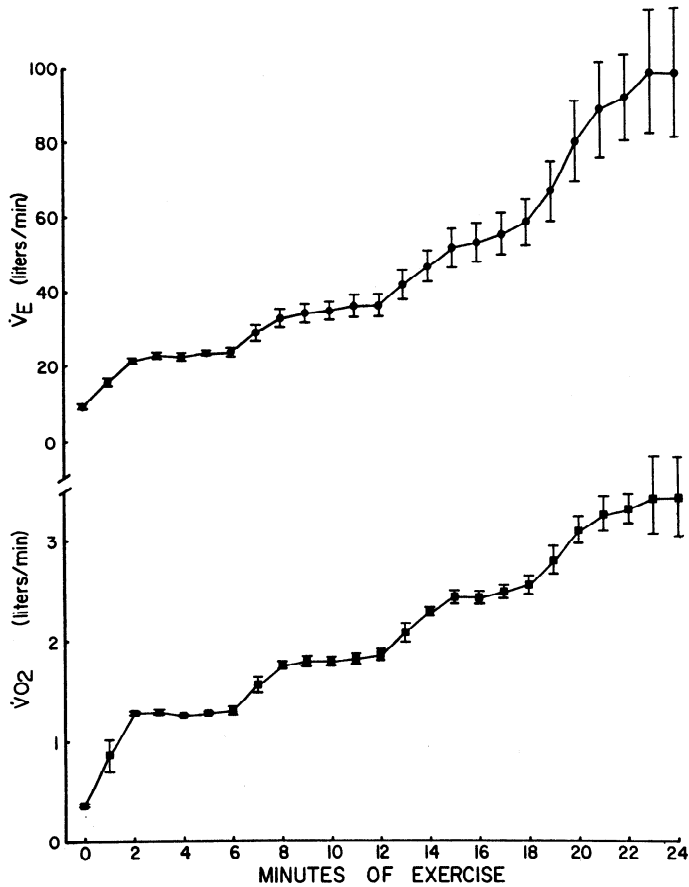


FIG. 1. Mean values (\pm SE) for ventilation (\dot{V}_E) and oxygen consumption ($\dot{V}O_2$) as a function of duration of exercise; $n = 6$ for all but final 2 data points at $1,200 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$ where $n = 3$.

Rates of appearance and disappearance. Near steady-state lactate turnover values were observed at rest. R_a and R_d were 14.4 ± 1.8 and $15.1 \pm 2.2 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. During the last 2 min of exercise at 300 and $600 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$, near steady-state values were also observed, as evidenced by an unchanging lactate concentration (Fig. 2) and specific activity (Fig. 3). R_a was 32.8 ± 2.3 and 59.1 ± 2.6 , and R_d was 37.4 ± 1.3 and $55.4 \pm 2.3 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at 300 and $600 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$, respectively (Fig. 2). R_a was significantly greater than R_d at both 900 and $1,200 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$. R_a and R_d averaged 145.4 ± 10.5 and $110.2 \pm 5.6 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during the last 2 min at 900 , and 309.4 ± 20.8 and $169.7 \pm 10.6 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during *min 3* and *4*, $1,200 \text{ kg} \cdot \text{m} \cdot \text{min}^{-1}$, the last time point completed by all subjects. All subjects showed a linear relationship between R_a and arterial lactate concentration (Table 2). A curvilinear relationship was observed between R_d and lactate concentration (Table 2, Fig. 4). The R_d was a linear function of the lactate concentration raised to the 0.5 power. A further effort to optimize the fit of the curve failed to result in a different exponent or a higher correlation coefficient. The slope of the tangent to this curve is the instantaneous MCR. Extremely high correlation coefficients were observed in the relationship between R_a and R_d and arterial lactate concentration (Table 2). However, this exceptional fit is inevitable because the calculation of both R_a and R_d involve arterial lactate concentration (see *Eqs. 1*

and 2). This is especially true at high lactate concentrations, where ΔSA is small (Fig. 3) and R_a and R_d are mainly determined by \bar{LA} and ΔLA . Large interindividual variations were observed in the slopes of the R_a and R_d lactate concentration relationships (Table 2). Subjects with low peak arterial lactate values had much higher R_a and R_d values for a given arterial lactate concentration than subjects with higher peak lactate concentrations (Fig. 4, Tables 1 and 2).

During graded exercise, R_a and R_d were exponentially related to $\dot{V}O_2$ for all subjects. Figure 5 shows the relationship between R_a , R_d , and lactate concentration and $\dot{V}O_2$ in a representative subject. This relationship was evident regardless of the V used in the calculation of R_a and R_d , even though the value of V used had a profound effect on the calculated R_a and R_d at high $\dot{V}O_2$ values (Fig. 6). The logarithms of R_a and R_d were linearly related to $\dot{V}O_2$ for a given subject (Table 3). The mean correlation coefficient was 0.989 for both parameters.

Metabolic clearance rate. The MCR was significantly above resting values throughout exercise (Fig. 2). The

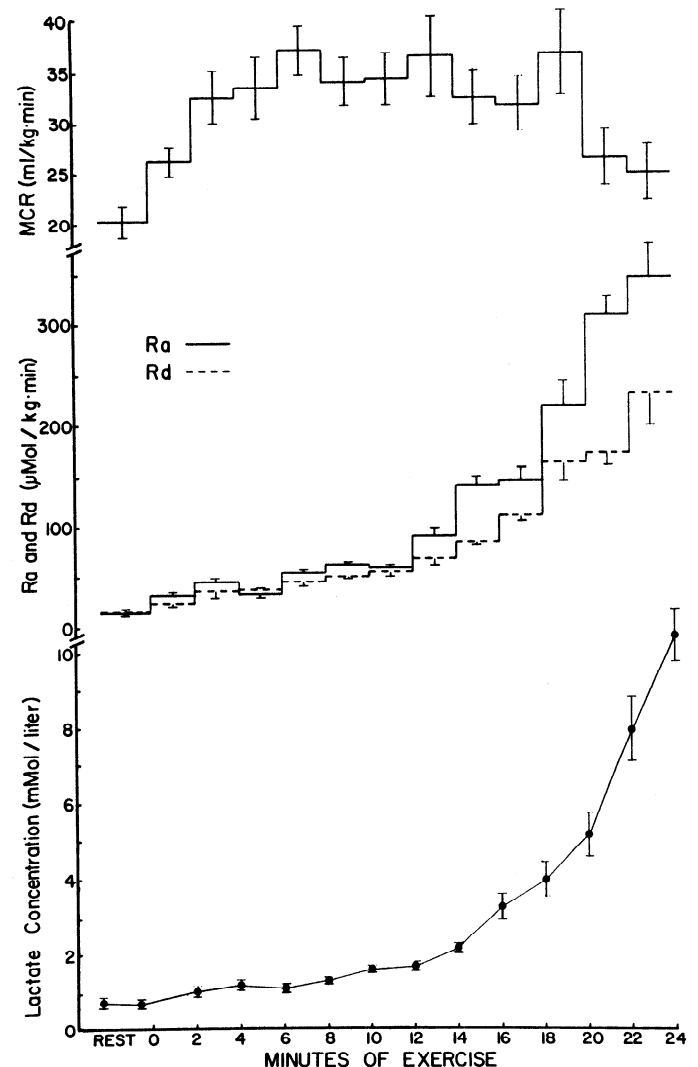


FIG. 2. Mean values for arterial lactate concentration, rate of lactate appearance (R_a) and disappearance (R_d), and metabolic clearance rate (MCR) as a function of time.

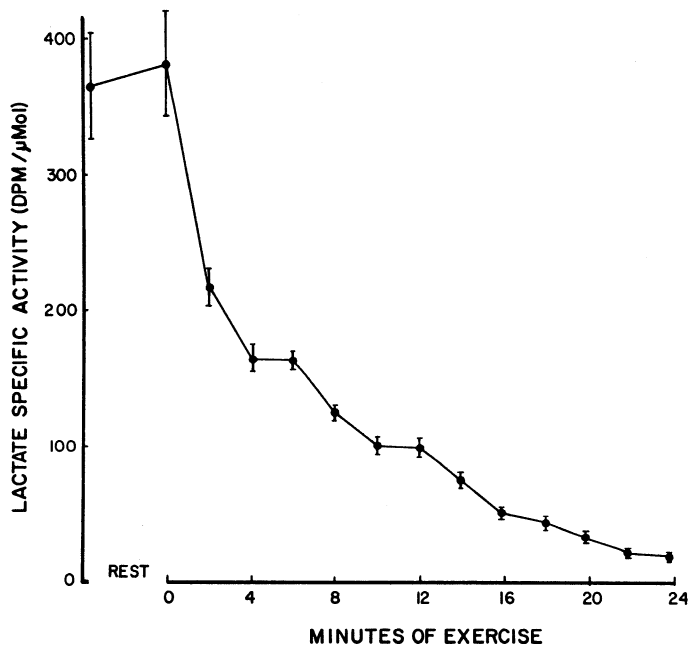


FIG. 3. Mean values for arterial lactate specific activity (dpm/ μ mol) as a function of duration of exercise.

TABLE 2. Equations for rates of lactate appearance and disappearance as a function of arterial lactate concentration

Subject	<i>b</i>	<i>a</i>	Correlation Coefficient
$R_a = \text{lactate (mM)} \times b + a$			
1	58.6	-13.5	0.993
2	46.7	-7.1	0.986
3	51.6	-15.0	0.995
4	38.4	+3.6	0.987
5	43.7	-11.1	0.975
6	37.8	-3.5	0.960
$R_d = \text{lactate (mM)}^{0.5} \times b + a$			
1	108.7	-67.6	0.999
2	97.4	-64.6	0.993
3	88.2	-54.7	0.995
4	65.2	-34.9	0.996
5	116.7	-101.2	0.997
6	85.2	-62.9	0.985

Rate of lactate appearance (R_a) and disappearance (R_d) are in $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

MCR was $20.6 \pm 1.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at rest and increased during exercise to $33.6 \pm 3.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $34.4 \pm 2.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during the last 2 min at 300 and 600 $\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$, respectively. MCR increased to a peak of $37.2 \pm 2.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during the first 2 min at 600 $\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$ and decreased to $26.5 \pm 2.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during *min* 3 and 4 at 1,200 $\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$. The drop in exercise MCR at 1,200 $\text{kg} \cdot \text{m} \cdot \text{min}^{-1}$ was chiefly accounted for by the increase in lactate concentration.

DISCUSSION

The present results demonstrate that both lactate appearance and disappearance increased exponentially with $\dot{V}O_2$ during continued, graded exercise in humans. We observed a strong positive relationship between lac-

tate appearance or disappearance and the arterial lactate concentration during progressive, graded exercise. The increase in circulating lactate concentration during graded exercise occurred because R_a increased more rapidly than R_d and thus was not due solely to a sudden increase in R_a .

The value of the volume of distribution of lactate (V)

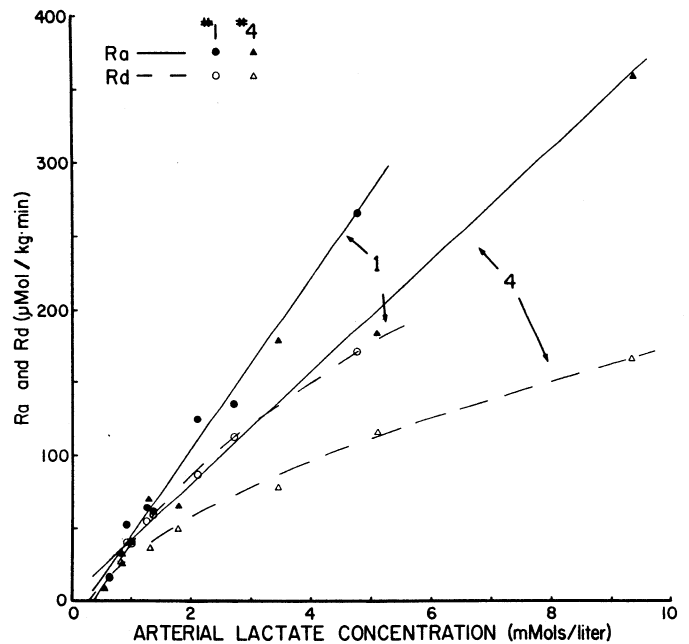


FIG. 4. Rates of lactate appearance (R_a) and disappearance (R_d) as a function of lactate concentration for subjects 1, a competitive runner, and 4, a recreational swimmer. See Table 2 for equations of lines and correlation coefficients.

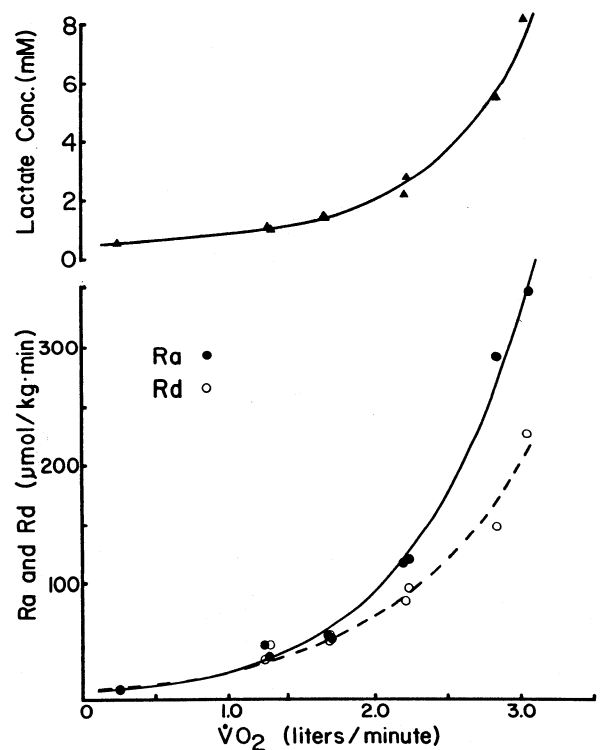


FIG. 5. Arterial lactate concentration and rates of lactate appearance (R_a), and disappearance (R_d) plotted as a function of oxygen consumption ($\dot{V}O_2$) in subject 2.

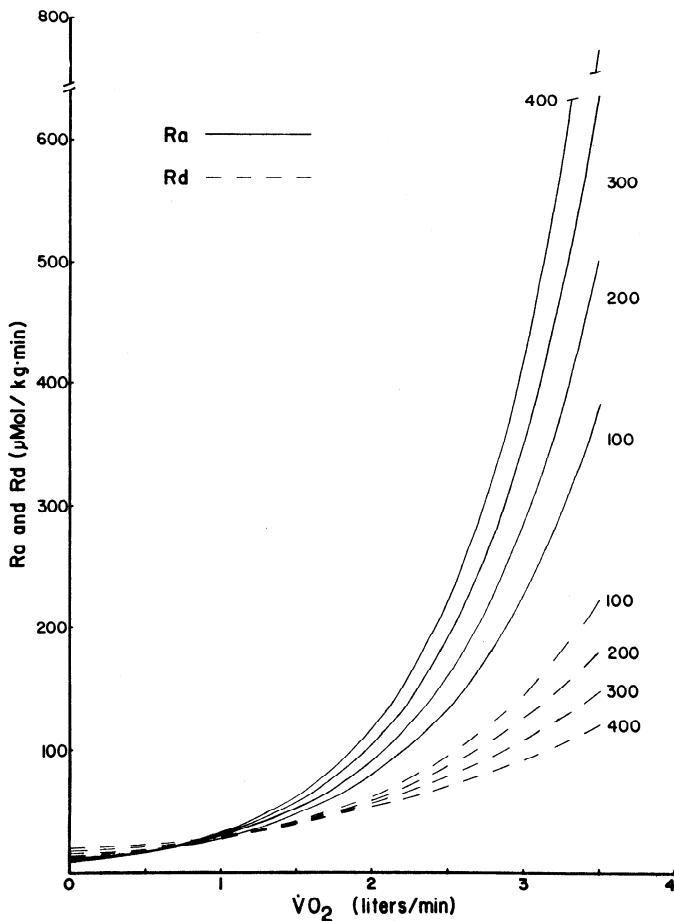


FIG. 6. Lines of best fit for mean rates of appearance (R_a) and disappearance (R_d) as a function of oxygen consumption ($\dot{V}O_2$) for volumes of distribution (V) values of 100, 200, 300, and 400 ml/kg.

greatly affects the calculated R_a and R_d in the two highest work loads (Fig. 6). Studies which attempted to determine the V in resting humans have calculated values ranging from 225 (28) to 494 ml/kg (31). No one has attempted to determine V during exercise or with exogenous lactate infusion to induce changes in lactate specific activity and concentration. Allsop et al. (1) infused glucose at various known rates into dogs with all sources of unlabeled glucose production surgically removed and found that during nonsteady states a time-variable "effective" volume of distribution of glucose was necessary to predict the R_a of glucose correctly from the equations of Steele (33). Rapid fluctuation in the R_a of glucose could be predicted reasonably well by using a fixed V of glucose of 40 ml/kg. Larger values gave greater errors. Wolfe (36) made similar measurements on dogs infused with urea and also concluded that the effective V for urea was not constant. A V of 100 ml/kg gave the least error between true and tracer-determined R_a of urea. Because, like urea, lactate is also not freely diffusible across membranes (13), one would expect a similarly small optimal fixed value for the volume of distribution of lactate.

The variable V supports the concept of a multicompartment model of lactate kinetics such as the two-compartment model described by Norwich (23). How-

ever, with the changes in metabolic rate elicited in the present study, it is extremely doubtful that the pool sizes and the rate constants for lactate exchange between compartments could be predicted with any accuracy. Even if they could be determined, it is doubtful that the two-compartment model would give much more accurate results than the simpler, one-compartment model described in the equations of Steele (33). Radziuk et al. (27) compared single and two-compartment models for the calculation of glucose R_a in dogs given a constant infusion of exogenous glucose. They observed similar errors in the absolute values of the areas between the calculated and infused glucose curves (9.5 and 8.4% for single and two-compartment methods, respectively). Therefore, we used the simple Steele (33) equations for the calculations of R_a and R_d .

From this discussion it should be clear that the "true lactate R_a " can not be accurately measured during heavy non-steady-state exercise due to lack of knowledge of the effective V . Because the results of Allsop et al. (1) and Wolfe (36) suggest that a small V (100 ml/kg or less) should give the best calculated R_a during changes in concentration and specific activity, we selected a V of 100 ml/kg for the presentation of our data. However, even if the "real" V was as large as 400 ml/kg, it would not affect our fundamental conclusions concerning the relationship between R_a or R_d and $\dot{V}O_2$. We observed exponential relationships between R_a and $\dot{V}O_2$ and R_d and $\dot{V}O_2$ regardless of the V selected (Fig. 6).

Our values for lactate turnover are comparable with previous reports on resting humans. We observed a lactate R_d of 15.1 $\mu\text{mol}/\text{kg}\cdot\text{min}$ at rest, which is similar to values previously reported. By use of [$U\text{-}^{14}\text{C}$]lactate, Searle and Cavalieri (31) and Kreisberg et al. (21) obtained values of 17.9 and 15.1 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively. Mazzeo et al. (22a) found the resting lactate disposal rate to be 22.9 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ as determined with a bolus injection of [$1\text{-}^{13}\text{C}$]lactate. Few determinations of the rate of lactate disappearance during exercise in humans have been made. Mazzeo et al. (22a), again

TABLE 3. Equations for rates of lactate appearance and disappearance as a function of oxygen consumption

Subject	b	a	Correlation Coefficient
$R_a = b^{\dot{V}O_2 (\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1})} \times a$			
1	1.076	10.00	0.994
2	1.083	7.24	0.993
3	1.074	9.77	0.997
4	1.097	7.24	0.987
5	1.061	12.59	0.968
6	1.077	11.22	0.993
$R_d = b^{\dot{V}O_2 (\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1})} \times a$			
1	1.062	12.02	0.997
2	1.067	9.12	0.993
3	1.062	10.72	0.982
4	1.072	8.91	0.981
5	1.046	16.98	0.983
6	1.061	12.88	0.997

Rate of lactate appearance (R_a) and disappearance (R_d) are in $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. $\dot{V}O_2$, O_2 consumption.

using a bolus of [^{13}C]lactate, found the lactate disposal rate to be 45.5 and 58.8 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at 50 and 75% $\dot{V}\text{O}_{2\text{max}}$, respectively. These values are calculated from data obtained from 20 to 65 min of exercise. Previously, we found the R_d of lactate after 25 min of supine cycle ergometer exercise at 40% of $\dot{V}\text{O}_{2\text{max}}$ to be 51.8 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in three men (32). We have observed the MCR of lactate to be 36.3 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ after 30 min of exercise at 40% of $\dot{V}\text{O}_{2\text{max}}$ in six men (35). The present investigation gave similar results (55.4 $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and 34.4 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for R_d and MCR, respectively) at 600 $\text{kg}\cdot\text{m}\cdot\text{min}^{-1}$, or roughly 40% of $\dot{V}\text{O}_{2\text{max}}$. Because in the present investigation the arterial blood lactate levels and specific activities determined during the 4th and 6th min at the two easier work loads (300 and 600 $\text{kg}\cdot\text{m}\cdot\text{min}^{-1}$) were not different within work loads (Figs. 2 and 3), these data can be considered as having been obtained at near a dynamic steady state.

Although we generally observed the R_a and R_d of lactate to increase linearly and curvilinearly, respectively, as a function of arterial lactate concentration (Table 2), there were disproportionate increases in R_a and R_d relative to lactate concentration at the onset of exercise. There was only a 54% increase in arterial lactate concentration despite a 128 and 148% increase in the R_a and R_d , respectively, from rest to the end of the first work load. The MCR of lactate increased by over 60%. Therefore, changes in arterial lactate concentration from rest to mild exercise do not necessarily reflect changes in lactate kinetics.

The increase in the R_a of lactate is the result of an increased glycolytic carbon flux due to greater recruitment of type IIb muscle fibers and greater adrenergic stimulation at higher work loads. Gollnick et al. (12) studied the glycogen depletion pattern in human muscle fiber types after exercise at 31, 64, and 84% of $\dot{V}\text{O}_{\text{max}}$. At the lower work load they observed no increase in circulating lactate concentration during exercise and a selected depletion of glycogen in type I fibers. As work intensity increased, so did the lactate concentration and glycogen depletion in type II fibers. This suggests that there is an increase in the recruitment of type IIb fibers that coincides with an increase in the rate of appearance of lactate. The time course of the increase in the circulating concentration of catecholamines appears to be similar to that of lactate during incremental exercise (22). Most recently, Issekutz (16) observed a decrease in the glycogenolytic rate, blood lactate concentration, and the rate of lactate appearance after β -adrenergic blockage in running dogs, supporting the theory that glycogenolysis is hormonally controlled during exercise by the interaction between epinephrine and β -adrenergic receptors. As described previously (7) norepinephrine could cause a decrease in R_d through the shunting of blood away from gluconeogenic organs (30).

The major site of lactate removal appears to be exercising skeletal muscle (6, 7, 14, 17, 19). Studies by Jorfeldt (19) on the exercising forearm indicate that exercising human skeletal muscle tissue both produces and extracts lactate during net lactate production. This suggests working muscle is both a site of lactate production

and removal during exercise. As suggested previously (4), this is most likely the result of the different metabolic characteristics of type I and IIb muscle fibers. Type IIb fibers, with high concentrations of glycolytic enzymes and M-LDH isozyme and a low mitochondrial content, produce lactate when stimulated (2, 25). On the other hand, type I fibers, with a greater fraction of H-LDH isozyme and a high mitochondrial content, more readily oxidize pyruvate and lactate during contraction. During exercise, lactate concentration is much higher in type IIb fibers than in type I fibers (2). Thus it is likely that lactate generated in one muscle fiber (e.g., by type IIb fibers) could be taken up and oxidized by another fiber (e.g., by type I and IIa fibers). Lactate released into the venous blood could also be extracted from the recirculated arterial blood on reperfusion of the active muscle and oxidized by type I and IIa fibers (2, 3). The other major sites of lactate removal during exercise are the liver (30) and the heart (20).

Our results suggest that the R_d is dependent on the lactate concentration and concomitantly on the R_a . As exercise intensity increased in the present experiment, R_a increased more rapidly than did R_d (Fig. 2). R_a exceeded R_d transiently at the beginning of easy exercise loads (e.g., 300 and 600 $\text{kg}\cdot\text{m}\cdot\text{min}^{-1}$) (Fig. 2). Most recently, Mazzeo et al. (22a) observed steady blood lactate levels and disposal at 70% of $\dot{V}\text{O}_{2\text{max}}$ in subjects who were injected with [^{13}C]lactate after 20 min of preliminary exercise. These results strongly suggest that R_d is a function of arterial lactate concentration and R_a . It appears that there is a time lag for a response in R_d after a change in R_a . Factors such as the circulatory distribution of lactate and the transport of lactate across membranes may be implicated.

The sites for infusion of lactate tracer and sampling of blood greatly affects the specific activity of lactate used in the calculation of R_a and R_d . Reilly and Chandrasena (29) continuously infused [$\text{U-}^{14}\text{C}$]lactate into a jugular vein in sheep and sampled blood from the opposite jugular vein and the carotid artery. The venous specific activity was 30% lower in the vein than the artery due to exchange of lactate across the tissues of the superior circulation. Freminet and Minaire (10) observed similar results in rats. It was concluded by Reilly and Chandrasena (29) that tracer should be infused venously and sampled arterially to allow for complete mixing of infused lactate with endogenous lactate before sampling. Okajima et al. (24) compared the aortic infusion with venacaval sampling method (A-V mode) to the venacaval infusion with arterial sampling method (V-A mode). They concluded that the tracer should be infused aortically and sampled in the vena cava. However, as they stated, they found no definite validation of the necessity for using the A-V mode over the V-A mode. The A-V mode was preferred merely because it resulted in a greater calculated lactate mass and space and greater rates of lactate turnover and recycling (24). In the present investigation, as in previous studies on exercising animals (6, 7, 8, 16, 17, 30), the V-A mode was used due to the necessity of adequate mixing of radioactive lactate with endogenous lactate, as demonstrated by Reilly and

Chandrasena (29) and Freminet and Minaire (10).

Results of the present investigation indicate that lactate R_a and R_d increase linearly and curvilinearly, respectively, as a function of lactate concentration (Table 2, Fig. 4). The relationship between R_a and arterial lactate concentration found in this study was similar to the relationship observed by Issekutz et al. (17) in dogs during prolonged constant rate treadmill running. Issekutz et al. (17) fitted a straight line to their data. However, visual inspection of their results suggests that a more appropriate fit is attained by a curvilinear line, as found in the present investigation.

We observed marked differences between subjects in the relationships between R_a and R_d , and lactate concentration (Table 2, Fig. 4). These differences reflect variability in the MCR or the slope in the R_d vs. lactate concentration relationship between subjects. In Fig. 4 the results for *subject 1*, a competitive long distance runner, are compared with *subject 4*, a recreational swimmer. It is apparent that lactate R_a and R_d are significantly higher in *subject 1* (the trained athlete) for a given arterial lactate level. The lower circulating lactate level in *subject 1* reflects a greater lactate MCR rather than a decrease in R_a . Previously, Donovan and Brooks (7) attributed lower circulating levels of lactate in endurance-trained rats during exercise to a greater MCR. The present results support the hypothesis that the lower lactate concentration in endurance-trained individuals can be largely attributed to an enhanced clearance of lactate from the blood, rather than solely to a decrease in the rate of lactate production.

It has been suggested that the sudden increase in lactate concentration during heavy work loads represents a threshold above which muscles produce lactate and reflects anaerobiosis in the muscle tissue and a shift in the redox state of the muscle cells (34). However, there is little experimental evidence for this model. Jobsis and Stainsby (18) used fluorometric techniques to study muscle mitochondrial NADH/NAD⁺ during contractions of dog muscle in situ. When muscle preparations were stimulated to contract at exercise intensities sufficient to

produce maximal O₂ consumption and a significant net efflux of lactate, the redox state of the muscle, reflected by the NADH/NAD⁺ ratio, was more oxidized than at rest. More recently, Connett et al. (5) used myoglobin cryomicroscopy techniques to determine the O₂ tension throughout dog gracilis muscle tissue contracting in situ. They did not find local areas of anoxia even during the transition from rest to exercise or during heavy work loads (70% VO_{2 max}). The minimum PO₂ in dog muscles studied by Connett et al. did not drop below 2 Torr, which is significantly above the critical mitochondrial O₂ tension (0.1–1.5 Torr). Despite the oxygenation of tissues, lactate accumulation and net release occurred, even during mild stimulation (10% VO_{2 max}). Pirnay et al. (26) observed that the PO₂ in deep femoral venous blood of humans during maximal leg exercise did not fall below 12 Torr. Even given β -receptor antagonists, deep femoral venous PO₂ did not fall below 10 Torr. During exercise at ~50% VO_{2 max}, the PO₂ values were approximately double those mentioned. The results of these investigations imply that lactate production can occur for reasons other than a lack of O₂ delivery to the mitochondria.

In conclusion, results of the present investigation demonstrate that the rates of lactate appearance and disappearance are positively correlated to arterial lactate concentration for a given individual. Lactate appearance and disappearance are exponential functions of VO₂ during graded exercise. The increase in circulating lactate concentration during progressive, graded exercise occurs because the rate of lactate appearance increases faster than the rate of lactate disappearance.

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