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ORIGINAL ARTICLE

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A study of lactate metabolism without tracer during passive and active postexercise recovery in humans

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Abstract Tracers have been used extensively to study lactate metabolism in humans during rest and exercise. Nevertheless, quantification of in vivo lactate kinetics as measured by lactate tracers remains controversial and new data are necessary to clarify the issue. The present study has developed a simple kinetic model which does not require labelled molecules and which yields proportional and quantitative information on lactate metabolism in humans during postexercise recovery performed at different levels of intensity. Five subjects took part in six experiments each of which began with the same strenuous exercise (StrEx; 1 min, 385 W, 110 rpm). The StrEx of each session was followed by a different intensity of recovery: passive recovery (PR) and active recoveries (AR) with power outputs of 60, 90, 120, 150 and 180 W, respectively. Blood lactate concentration was measured prior to and immediately after StrEX and regularly during the 1st h of recovery. Oxygen uptake ($\dot{V}O_2$) was measured every 30 s during the whole session. The results showed that the disappearance rate constant (k_e) increases abruptly from PR [0.080 (SEM 0.004) min^{-1}] to moderate AR [60 W: 0.189 (SEM 0.039) min^{-1}] and decreases slowly during more intense AR [180 W: 0.125 (SEM 0.027) min^{-1}]. The lactate apparent clearance ($Cl \cdot F^{-1}$) was calculated from the area under the lactate concentration-time curve. The $Cl \cdot F^{-1}$ increased 1.81 (SEM 0.17) fold from PR to moderate AR (60 W) and only 1.31 (SEM 0.14) from PR to the most intense AR (180 W). Using the model, the apparent lactate production ($F''K_0$) was also calculated. The $F''K_0$ increased regularly following a slightly curvilinear function of $\dot{V}O_2$ and was 2.61 (SEM 0.53) fold greater during the most intense AR (180 W) than during PR. Because of the lack of data concerning the size of apparent lactate distribution volume (V_d), the apparent turnover rate (R_{bl}) has been presented here related to V_d. The $R_{bl} \cdot V_d^{-1}$ increased also following a slightly curvilinear function of $\dot{V}O_2$. The $R_{bl} \cdot V_d^{-1}$ was 85.90 (SEM 14.42) $\mu mol \cdot min^{-1} \cdot l^{-1}$ during PR and reached 314.09 (SEM 153.95) $\mu mol \cdot min^{-1} \cdot l^{-1}$ during the most intense AR (180 W). In conclusion the model presented here does not require labelled molecules and firstly makes it possible to follow the proportional change of apparent lactate clearance and apparent lactate production during active postexercise recovery in comparison with passive recovery conditions and secondly to estimate the blood lactate turnover.

Key words Modelling · Lactate turnover · Lactate clearance

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Introduction

Tracers have been used extensively to study lactate metabolism in humans during rest and exercise (Katz and Wolfe 1988; MacRae et al. 1992; Mazzeo et al. 1986; Searle and Cavalieri 1972; Stanley et al. 1985, 1986, 1988). However, as discussed by Sahlin (1987), these data should be taken with caution because of the rapid interconversion between lactate and pyruvate. Recently, to evaluate the extent of this interconversion, Zhang et al. (1993) have infused six anaesthetized dogs with 1-^{13}C-lactate and U-^{13}C-pyruvate. Their results have indicated that the conversion is so complete that the blood pyruvate and lactate pools can probably be considered as one. Therefore, tracer techniques using labelled lactate cannot distinguish between pyruvate and lactate metabolism and thus more complex modelling is necessary for the quantification of lactate kinetics alone.

Another problem in quantifying lactate metabolism with tracers is the selection of the appropriate infusion

and sampling sites. In 1981, Okajima et al. published a study of lactate turnover in rats, using [^{14}C]- and [^{3}H] lactate. Two methods of tracer administration were performed: (1) injection into vena cava and sampling from aorta (v-a mode) and (2) injection into aorta and sampling from vena cava (a-v mode). The results obtained differed markedly according to the procedure. Lactate turnover in rats obtained with [^{14}C] lactate was 94.4 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ and 62 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ for a-v and v-a modes, respectively. In his recent review, Katz (1992) has written that "*in all animal species examined (rat, rabbit, dog, sheep and humans) the turnover of lactate, as determined in the A-V mode, ranged from 25% to 50% higher than in the V-A mode*". He thought also that the a-v mode would underestimate true lactate turnover only by 5%–10%.

Contrary to Binder et al. (1991), the common procedure for measuring the lactate turnover (the turnover is the ratio of the rate of infused tracer to that of the specific activity of the trace in the blood) using the v-a mode has a precise physiological meaning. It measures the turnover rate of lactate that passes through the circulation, whereas the lactate turnover rate calculated with the a-v mode always overestimates the turnover rate of circulating lactate and bears no direct relationship to the turnover in the whole body.

It seems thus that the quantification of in vivo lactate kinetics as measured by lactate tracers remains unclear and that new data are necessary to clarify the issue. The purpose of the present study was to propose a kinetic model which does not require labelled molecules and which yields proportional and quantitative information on lactate metabolism in humans during the 1st h of passive and active recoveries.

Methods

Subjects

Lactate kinetics was studied in five healthy male volunteers. All the subjects were physical education students. They were first informed about the experiment protocols and then, their consent was obtained. Their main characteristics are listed in Table 1.

Protocols

Six experiments were performed by five subjects. Each session began with a strenuous exercise (StrEX) performed on a Monark friction loaded cycle ergometer. The duration of StrEx was fixed at 1 min, the power output at 385 W and the pedalling frequency at 110 rpm. The intention of StrEx was to load the subject with a large amount of endogeneous lactate. The StrEx was followed by a different intensity of recovery: passive recovery (PR) and active recoveries (AR) with power outputs of 60, 90, 120, 150 and 180 W. The aim of these protocols was to analyse the kinetics of lactate initially produced as a function of various metabolic rates during the recovery period and then, to draw conclusions concerning lactate metabolism related to the intensity of recovery exercise.

Table 1 Subjects characteristics

Subjects	Age (years)	Height (cm)	Body mass (kg)	Maximal O_2 uptake ($l \cdot min^{-1}$)
1	23	180	76	3.906
2	21	186	81	3.165
3	23	179	74	4.819
4	21	186	83	5.268
5	20	184	78	4.892

Blood lactate concentration was determined from an ear lobe blood sample using the Yellow Spring Instrument method (YSI model 23L lactate). Blood samples were taken prior to StrEx, immediately after StrEx and at the 2nd, 4th, 6th, 8th, 10th, 12.5th, 15th, 20th, 25th, 30th, 35th, 40th, 45th, 50th, 55th, and 60th min following StrEx. This recovery duration was long enough to reach a steady-state blood lactate concentration. All lactate kinetic parameters were computed in accordance with the model presented below. Oxygen uptake ($\dot{V}O_2$) was measured at rest and every 30 s during and after StrEx. To estimate the $\dot{V}O_2$ corresponding to the metabolic rate due to the recovery intensity ($\dot{V}O_{2ss}$), $\dot{V}O_2$-time data during the recovery period were fitted with a function containing two exponentials and one base-line:

$$\dot{V}O_2 = A \cdot e^{-a\,t} + B \cdot e^{-b\,t} + \dot{V}O_{2ss}$$

Model

Based on a model presented and validated elsewhere (Francaux et al. 1993), the equations below describe the lactate concentration time-course from the start of short and strenuous exercise up to the end of passive or active recoveries performed at different levels of intensity.

Equations describing the lactate concentration at the steady state

One may consider that blood lactate concentration at steady state ($[la^-]_{b,ss}$) represents an equilibrium between lactate production and elimination. This can be expressed by the following equation:

$$dQ/dt = K_0 - k_e \cdot Q \quad (1)$$

where K_0 is a zero order rate constant which describes the constant production of lactate at steady state; k_e is a first order rate constant which describes the disappearance of lactate from the blood compartment; Q is the amount of lactate in the body.

Since at steady state dQ/dt is equal to 0, Eq. 1 yields directly:

$$Q_{ss} = K_0/k_e \quad (2)$$

where Q_{ss} is the amount of lactate in the body at steady state.

If one assumes that there is a constant relationship between blood lactate concentration $[la^-]_b$ and the amount of lactate in the body (Q):

$$Q = [la^-]_b \cdot V_d \quad (3)$$

where V_d is the lactate distribution volume.

The relationship between $[la^-]_b$ and lactate amount in the body as expressed by Eq. 3 allows the conversion of Eq. 2 from an amount-time to a concentration-time relationship which may be expressed as:

$$Q_{ss}/V_d = K_0/(k_e \cdot V_d) \quad (4)$$

Because all the lactate produced does not appear in the blood compartment (Freund and Zouloumian 1981b), a proportionality constant (F') must be applied to Eq. 4 to give:

$$(F' \cdot Q_{ss})/V_d = [la^-]_{b,ss} = (F' \cdot K_0)/k_e \cdot V_d) \quad (5)$$

where $[la^-]_{b,ss}$ is the blood lactate concentration at steady state.

Equations describing $[la^-]_b$ time course due to short and strenuous exercise

Immediately after the start of short and strenuous exercise, $[la^-]_b$ increases to reach a peak after the first few minutes of recovery. It then decreases following an exponential time function. This figure integrates lactate production, lactate appearance into the blood and lactate disappearance from the blood. This phenomenon may be represented by the following equation:

$$dQ/dt = k_a \cdot Q_{prod} - k_e \cdot Q \quad (6)$$

where k_a is a first order rate constant which accounts for lactate appearance into the central compartment; Q_{prod} is the amount of lactate at the production site.

After integration, Eq. 6 becomes:

$$Q_t = Q_0 \cdot (k_a/(k_a - k_e)) \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t}) \quad (7)$$

where Q_t is the amount of lactate in the central compartment at time t; Q_0 is the amount of lactate produced during StrEx.

Based on Eqs. 3 and 7, the lactate concentration due to the StrEx (C'_t) may be described by the following equation:

$$C'_t = (Q_0/V_d) \cdot (k_a/(k_a - k_e)) \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t}) \quad (8)$$

Because all lactate produced does not appear in the central compartment, a proportionality constant (F) must also be applied to Eq. 8 to give:

$$C'_t = (FQ_0/V_d) \cdot (k_a/(k_a - k_e)) \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t}) \quad (9)$$

Combining Eqs. 5 and 9, one obtains:

$$C_t = (FQ_0/V_d) \cdot (k_a/(k_a - k_e)) \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t}) + (F' \cdot K_0)/(k_e \cdot V_d) \quad (10)$$

This equation describes the lactate concentration (C_t) from the start of StrEx up to the end of the recovery. It takes into account the lactate kinetics due to the StrEx alone and the C_t associated with steady-state exercise $[la^-]_{b,ss}$ or with rest. Equation 10 may also be expressed:

$$C_t = (FQ_0/V_d) \cdot (k_a/(k_a - k_e)) \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t}) + [la^-]_{b,ss} \quad (11)$$

Actually, the model described above is an open one-compartment model applied to lactate kinetics. In such a model the k_e is an apparent constant which is the ratio between clearance (Cl) and (V_d)

$$k_e = Cl/V_d \quad (12)$$

Integration of Eq. 11 from 0 to inifinity yields:

$$\int_{t=0}^{t=\infty} (C_t - [la^-]_{b,ss})\,dt = (FQ_0/V_d) \cdot [k_a/(k_a - k_e)] \cdot [(1/k_e) - (1/k_a)]$$

$$= AUC \quad (13)$$

This equation gives the area under the lactate concentration-time curve (AUC) due only to the StrEx. Rearrangement of Eq. 13 yields:

$$AUC = FQ_0/(V_d \cdot k_e) = FQ_0/Cl \quad (14)$$

Using this model, the ratio between AUC of two different recovery periods in the same subject gives:

$$AUC_1/AUC_2 = (F_1 Q_{0,1}/Cl_1) \cdot (Cl_2/F_2 Q_{0,2}) \quad (15)$$

If one assumes that $Q_{0,1}$ and $Q_{0,2}$ are equal because of the same initial exercise, the ratio between AUC yields the ratio between apparent lactate clearances ($Cl \cdot F^{-1}$):

$$AUC_1/AUC_2 = (F_1/Cl_1) \cdot (Cl_2/F_2) = (Cl_2 \cdot F_2^{-1})/(Cl_1 \cdot F_1^{-1}) \quad (16)$$

The same approach may be applied to $[la^-]_{b,ss}$ values:

$$[la^-]_{b,ss,2}/[la^-]_{b,ss,1} = (F_2 K_{0,2}/Cl_2) \cdot (Cl_1/F_1 K_{0,1}) \quad (17)$$

Combining Eqs. 16 and 17, one obtains:

$$(AUC_1/AUC_2) \cdot ([la^-]_{b,ss,2}/[la^-]_{b,ss,1})$$
$$= (F_1/Cl_1) \cdot (Cl_1/F_1' K_{0,1}) \cdot (Cl_2/F_2) \cdot (F_2' K_{0,2}/Cl_2) \quad (18)$$

After rearrangement:

$$(AUC_1/AUC_2) \cdot ([la^-]_{b,ss,2}/[la^-]_{b,ss,1}) = (F_2' K_{0,2}/F_1' K_{0,1}) \cdot (F_1/F_2) \quad (19)$$

If $F' \cdot F^{-1}$ is equal to F'', $F' K_0 F^{-1}$ is noted $F'' K_0$ and is called apparent rate of lactate production. Then:

$$(AUC_1/AUC_2) \cdot ([la^-]_{b,ss,2}/[la^-]_{b,ss,1}) = F_2'' K_{0,2}/F_1'' K_{0,1} \quad (20)$$

Equation 20 yields the ratio between the apparent rates of lactate production during different exercise intensities.

On the other hand, at steady-state concentrations, the blood lactate turnover (R_{bl}) is equal to $[la^-]_{b,ss}$ times clearance:

$$R_{bl} = [la^-]_{b,ss} \cdot Cl \quad (21)$$

Knowing Eq. 12, $R_{bl} \cdot V_d^{-1}$ may be calculated as follows:

$$R_{bl} \cdot V_d^{-1} = k_e \cdot [la^-]_{b,ss} \quad (22)$$

Statistical analysis

The fit of the theoretical curves has been computed using MINSQ following the Simplex nonlinear regression method (derivative-free methods) described by Nedler and Mead (1965). The StrEx started at time 0. The first datapoint immediately after StrEx was considered to be time 1 and so on until 61 min after the beginning of StrEx. The statistics have been computed using SYSTAT (Wilkinson, Leyland 1989).

Results

Oxygen uptake

The base-line of the $\dot{V}O_2$-time curve represents $\dot{V}O_2$ due to the intensity of recovery ($\dot{V}O_{2,ss}$) (Table 2). As expected, $\dot{V}O_{2ss}$ increased linearly with power output ($\dot{V}O_{2ss} = 303.3 + 13.29\ W$; $r^2 = 0.938$).

Lactate kinetics

After an initial increase during StrEx, $[la^-]_b$ still increased at the beginning of each recovery to reach a peak. It then decreased according to an exponential function of time. All lactate kinetics were fitted using Eq. 11 of the model and always gave a very satisfactory

Table 2 Steady-state oxygen uptake corresponding to the metabolic rate during the recovery period ($\dot{V}O_{2ss}$) and kinetics parameters of lactate recovery. k_e disappearance rate constant, k_a appearance rate constant, FQ_0/V_d lactate amount appearing in the blood compartment divided by the volume of distribution space, $[la^-]_{b,ss}$ steady state blood lactate concentration induced by the intensity of the recovery, AUC area under the blood lactate concentration-time curve

		Rest	60 W	90 W	120 W	150 W	180 W
$\dot{V}O_{2ss}$	Mean	330.70	1120.70	1472.80	1857.02	2214.54	2798.20
(ml·min^{-1})	SEM	28.95	52.70	102.89	83.97	93.89	162.54
k_e	Mean	0.080	0.189	0.166	0.157	0.134	0.125
(min^{-1})	SEM	0.004	0.039	0.036	0.027	0.029	0.027
k_a	Mean	0.801	0.502	0.633	0.688	0.736	0.572
(min^{-1})	SEM	0.161	0.094	0.077	0.069	0.118	0.101
FQ_0/V_d	Mean	9.74	11.58	10.97	11.61	9.70	9.47
(mmol·l^{-1})	SEM	1.07	1.18	0.97	0.47	0.76	0.56
$[la^-]_{b,ss}$	Mean	1.05	0.89	0.84	1.11	1.40	2.12
(mmol·l^{-1})	SEM	0.13	0.18	0.12	0.20	0.24	0.54
AUC	Mean	122.17	71.83	75.22	82.75	87.11	96.17
(mmol·min·l^{-1})	SEM	15.50	12.95	12.10	12.13	14.22	16.73

fit (Fig. 1). Results of kinetic parameters are presented in Table 2 and illustrated in Fig. 2.

The k_e mean (Table 2) increased abruptly from PR [0.080 (SEM 0.004) min^{-1}] to moderate AR [60 W: 0.189 (SEM 0.039) min^{-1}] and then decreased slowly during more intense AR [180 W: 0.125 (SEM 0.027) min^{-1}]. A nonparametric Friedman test showed a significant difference between sessions ($P = 0.007$).

The estimated values of k_a were relatively constant during the six conditions of recovery. The Friedman test showed no significant difference between conditions of recovery.

The $FQ_0 \cdot V_d^{-1}$ is the lactate concentration that would be observed, at time zero, if the amount of lactate reaching the blood was in i.v. bolus distributed instantaneously. This parameter is not influenced by the appearance and disappearance rate constants. It remained relatively constant during the six sessions. The Friedman test showed no significant difference between conditions of recovery.

The AUC decreased markedly from PR [122.17 (SEM 15.50) mmol·min·l^{-1}] to moderate AR [60 W: 71.83 (SEM 12.95) mmol·min·l^{-1}] and then increased slowly with more strenuous exercise [180 W: 96.17 (SEM 16.73) mmol·min·l^{-1}]. The Friedman test showed significant differences between conditions of recovery ($P = 0.020$). Using Eq. 16, the $Cl \cdot F^{-1}$ may be calculated. The $Cl \cdot F^{-1}$ increased 1.81 (SEM 0.17) fold

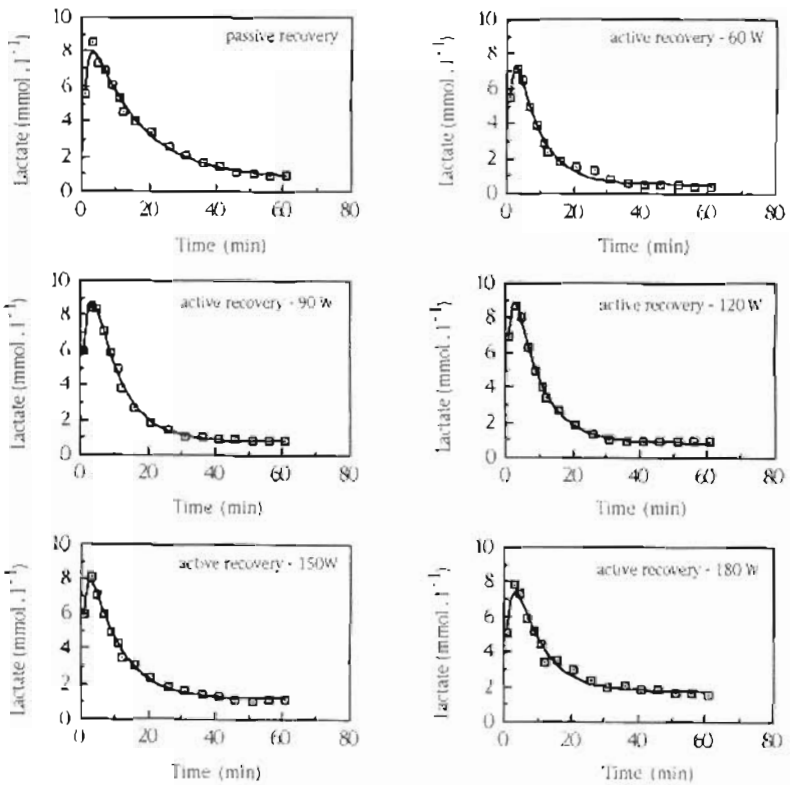

Fig. 1 Typical time courses of the blood lactate concentrations for different types of recovery observed in one individual

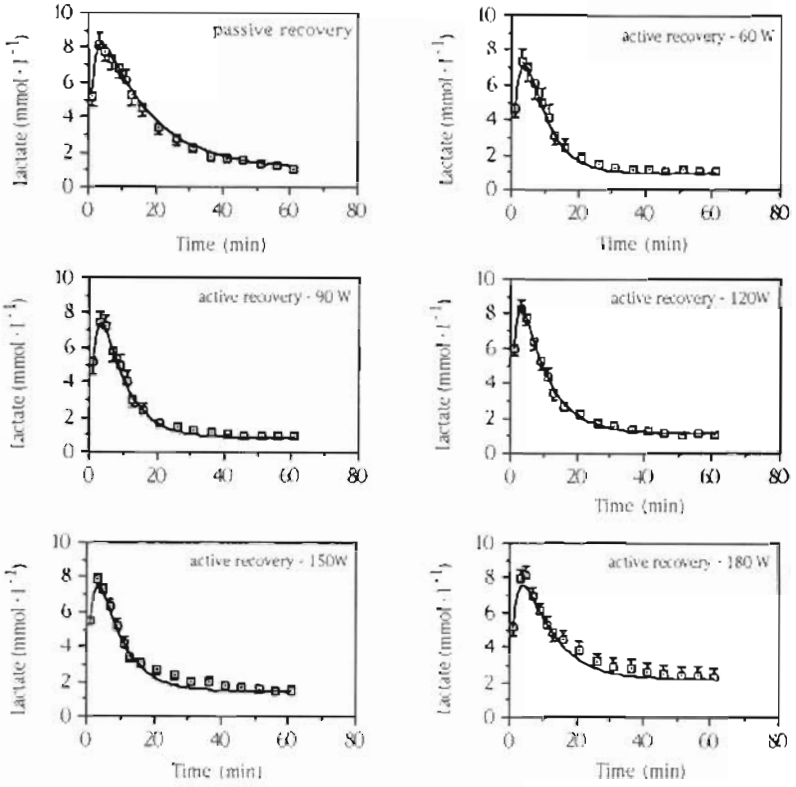

Fig. 2 Mean time courses of the blood lactate concentrations (mean and SEM) for different types of recovery ($n = 5$)

from PR to moderate AR (60 W) and only 1.31 (SEM 0.14) fold from PR to the most intense AR (180 W; Fig. 3).

The $[la]_{b,ss}$ induced by the intensity of recovery decreased slightly from PR [1.05 (SEM 0.13) mmol·l^{-1}] to moderate AR [90 W: 0.84 (SEM 0.12) mmol·l^{-1}] and then increased to 2.12 (SEM 0.54) mmol·l^{-1} during the most intense AR (180 W) (Table 2).

Knowing AUC and $[la]_{b,ss}$, the $F''K_0$ during PR and during AR may be calculated using Eq. 20 (Table 3). This ratio increased regularly following a slightly curvilinear function of $\dot{V}O_2$ (Fig. 4). The $F''K_0$ was 2.61 (SEM 0.53) fold greater during the most intense AR (180 W) than during PR.

Another method to estimate the lactate production during PR and AR consists of calculating R_{bl} using Eq. 22. Nevertheless, because of the lack of data concerning V_d and its possible variations during exercise, the results of R_{bl} have been presented related to V_d (Fig. 5). The $R_{bl} \cdot V_d^{-1}$ increased also following a slightly curvilinear function of $\dot{V}O_2$. The $R_{bl} \cdot V_d^{-1}$ was 85.90 (SEM 14.42) µmol·min^{-1}·l^{-1} during PR and reached 314.09 (SEM 153.95) µmol·min^{-1}·l^{-1} during the most

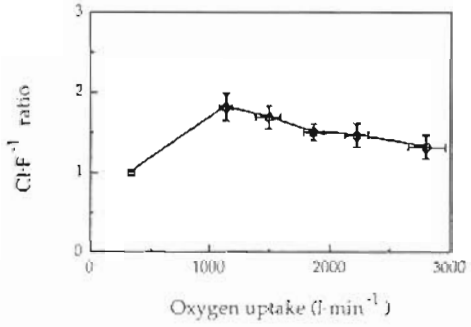

Fig. 3 Lactate apparent clearance ($Cl \cdot F^{-1}$) ratio versus oxygen uptake

Table 3 Apparent lactate production ratio ($F''K_0$) and apparent blood lactate turnover by unit of distribution volume ($R_{bl} \cdot V_d^{-1}$), at rest and during exercise

		Rest	60 W	90 W	120 W	150 W	180 W
$F''K_0$ ratio	Mean	1	1.45	1.37	1.58	1.96	2.61
	SEM	0	0.11	0.17	0.18	0.31	0.52
$R_{bl} \cdot V_d^{-1}$ (µmol·min^{-1}·l^{-1})	Mean	85.90	163.13	132.95	184.55	205.46	314.09
	SEM	14.43	42.03	22.67	58.35	80.89	153.95

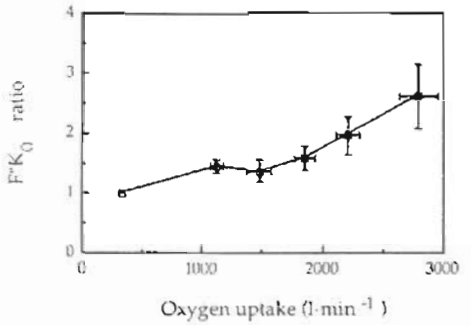

Fig. 4 Lactate apparent production ($F''K_0$) ratio versus oxygen uptake

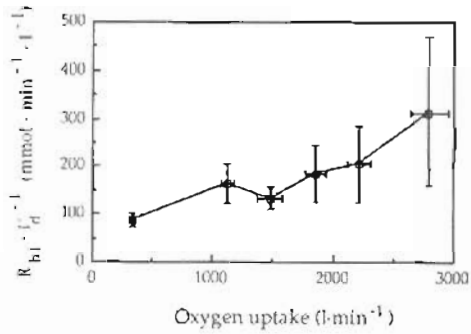

Fig. 5 Blood lactate turnover divided by the volume of the distribution space ($R_{bl} \cdot V_d^{-1}$) versus oxygen uptake

intense AR (180 W). However, great interindividual variations were observed for the $R_{bl} \cdot V_d^{-1}$ values. In particular, subject 3 presented for the six experiments a value of $R_{bl} \cdot V_d^{-1}$ markedly higher than the other subjects. This explains the large standard errors observed for the means of $R_{bl} \cdot V_d^{-1}$ (Table 3). Without taking subject 3 into consideration the mean value of $R_{bl} \cdot V_d^{-1}$ would be 72.36 (SEM 6.46) μmol · min^{-1} · l^{-1} during PR and 162.17 (SEM 32.16) μmol · min^{-1} · l^{-1} during the more intense AR (180 W).

Discussion

In 1981, Freund and Zouloumian (1981a) have presented a kinetic model to describe lactate kinetics in blood. This model is an open two-compartment model with elimination constants applied to both compartments (Fig. 6). The mathematical solution of that model leads to an equation that can accurately describe the concentration-time profile of lactate in the blood after exercise (Fig. 6). However, as far as the absolute values of the micro-constants are concerned (elimination rate constants, transfer rate constants, central and working muscle volumes of distribution space), the model cannot be solved in practice and partially loses its interest.

Based on that approach, we have used a simpler model in which the parameters would be directly meaningful and useful in practice. The model presented here is based on the pharmacokinetic theory. It is an open one-compartment model with vascular and extravascular administrations. In fact, it is a simplification of the model suggested by Freund and Zouloumian (1981a). The major difference is that the site of lactate production is represented in this model by a virtual compartment instead of real transfer compartment (Fig. 6). At rest lactate production is represented by a zero order rate constant from a virtual compartment of lactate production to the central compartment (intravenous infusion in pharmacokinetics). After short and strenuous exercise it is assumed that lactate is produced at once in a virtual compartment and released from that virtual compartment into the central compartment following a first order rate constant (oral or intramuscular administration in pharmacokinetics).

Lactate, as for many drugs, does not reach the blood completely. A fraction is metabolised in situ (in the virtual compartment). Therefore, a proportional factor F (bio-availability in pharmacokinetics) is used to express the in situ metabolism (first pass effect in pharmacokinetics). The mathematical solution of this model leads to parameters that can be interpreted as follows: k_a is the appearance rate constant of lactate into the central compartment. k_e is the disappearance rate constant of lactate from the central compartment. FQ_0/V_d is the fraction of the total amount of lactate produced during the strenuous exercise that reaches effectively the central compartment divided by the volume of the distribution space of the central compartment. The $[la^-]_{b,ss}$ is the result of the equilibrium between a constant appearance of lactate into the blood ($F' \cdot K_0$) and its disappearance from the blood. As shown in Fig. 6, the mathematical solution of that model leads to an equation (Eq. 11) that can accurately describe the blood lactate-concentration time profile and have a quality of fit similar to that obtained with the Freund and Zouloumian (1981a) equation. Nevertheless, in this equation, the time 0 is considered to be the onset of the recovery period whereas in the model presented here, the time 0 is the start of the StrEx.

Just after StrEx, the $[la^-]_b$ was already much higher than the lactate concentration at rest. This clearly indicates that lactate appearance in the blood circulation occurs between the start and the end of the StrEx. The delay between the start of the StrEx and the appearance of lactate in the blood circulation has been calculated as a few seconds ($\pm$ 6 s) by introducing in Eq. 11 a time lag parameter (t-time lag). Because the time lag was very small and did not improve significantly the quality of the fit, and in order not to lose a degree of freedom, it was decided not to use it and to consider the start of the StrEx as the time 0 of the analysis.

The results of the present investigation showed that the lactate disappearance rate constant (k_e) increased

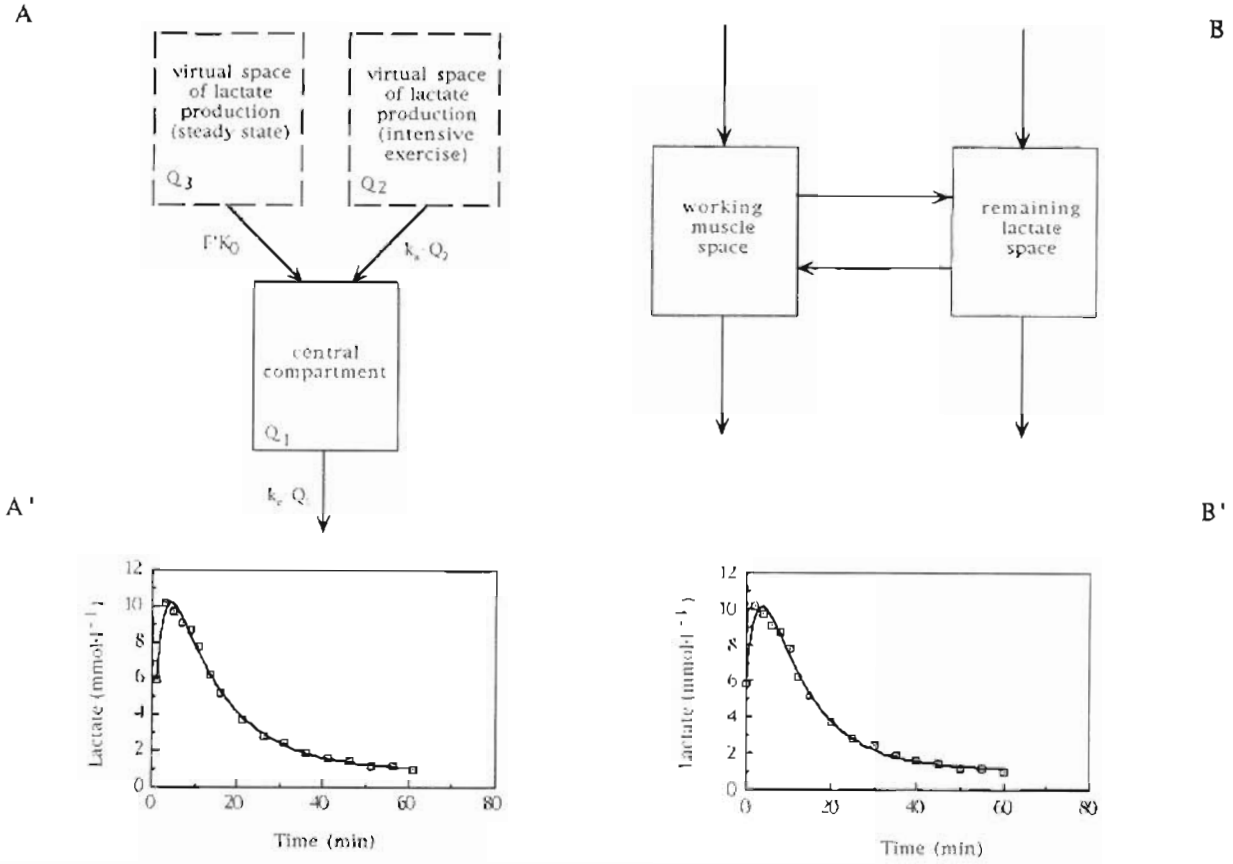

Fig. 6 (**A**) Open one-compartment model proposed in the present study and (**A'**) typical fit obtained using Eq. 11 ($r^2 = 0.994$). (**B**) Open two-compartment model proposed by Freund and Zouloumian (1981a) and (**B'**) fit of the same datapoints using the equation described by these authors ($r^2 = 0.966$). K_0 is the constant lactate production at steady state (zero order, mmol·min^{-1}), F is the bio-availability, k_a and k_e are the appearance and the disappearance rate constants (first order, min^{-1}), respectively, and Q_1, Q_2, Q_3 are lactate amounts (in millimoles)

from passive recovery [0.080 (SEM 0.004) min^{-1}] to moderate exercise recovery [60 W: 0.189 (SEM 0.039) min^{-1}] and decreased from moderate exercise recovery to intense exercise recovery [0.125 (SEM 0.027) min^{-1}; Table 2]. These variations are in good agreement with other studies which have examined lactate removal during various intensities of recovery (Belcastro and Bonen 1975; Dodd et al. 1984; Francaux et al. 1993; Hermansen and Stensvold 1972; Stamford et al. 1981; Weltman et al. 1979).

As, the StrEx was always the same, it was assumed that the amount of lactate produced (Q_0) during the StrEx was constant in each subject. An indirect method of verifying this assumption was to examine the differences in lactate concentration at the end of StrEx for each individual among the different trials. The Friedman test did not show any differences among trials and therefore confirmed that Q_0 was in all likelihood constant in each subject. The reason why StrEx was performed was to stimulate a large production of lactate during a brief period (1 min) which was considered as an endogeneous load of lactate. During recovery (60 min), lactate was produced and removed according to the intensity of the recovery exercise. If the lactate amounts produced initially during StrEx were always identical in the same subject, the variations of lactate kinetic parameters during the different recoveries may be interpreted as being variations due to the recovery exercise only. Therefore these kinetic parameters yielded information on lactate metabolism for the exercise intensity of each recovery. Considering this assumption, the major contribution of the present study was to estimate the R_{bl} without using labelled molecules. The R_{bl} is calculated from $[la^-]_{b,ss}$ and k_e. As k_e has been shown to be dependent on the intensity of the previous exercise (Freund et al. 1986), the R_{bl} values reported here should not be extrapolated to other exercise situations. Nevertheless, as StrEx was standardized, the changes in R_{bl} values here depend on the intensity of the recovery exercise.

The k_e is the ratio between Cl and V_d (Eq. 12). Thus, all k_e changes could be interpreted as a variation of Cl and/or V_d. The increase of k_e from PR to moderate AR was probably the consequence of an higher clearance. Nevertheless, because of the lack of data concerning V_d and its possible variation during exercise, a better

method to approach Cl is to calculate AUC which is the ratio between FQ_0 and Cl (Eq. 14).

If one assumes that Q_0 is constant due to the same initial exercise (StrEx), AUC changes are inversely proportional to $Cl \cdot F^{-1}$ changes. Thus, F is the factor which determines the fraction of lactate amount produced in the muscle that reaches the central compartment. This parameter (1-F) could be regarded as a muscle first pass effect during and after StrEx which may be linked to Cl. So, $Cl \cdot F^{-1}$ is called apparent lactate clearance. Considering AUC, $Cl \cdot F^{-1}$ increased abruptly [1.81 (SEM 0.17) fold] from PR to moderate AR (60 W) and then decreased slowly during more intense AR (Fig. 3). A similar change of k_e and AUC showed that V_d probably did not vary during long-term exercise (60 min).

These observations of lactate clearance changes during exercise are in good agreement with other studies either having used labelled molecules (MacRae et al. 1992; Mazzeo et al. 1986; Stanley et al. 1985) or not (Francaux et al. 1993). The reason why the lactate elimination is limited during exercise remains unclear.

On the other hand, the $[la^-]_{b,ss}$ induced by the recovery exercise intensity decreased slightly from PR and then increased during the heavier AR (Table 2). On basis of $Cl \cdot F^{-1}$ and $[la^-]_{b,ss}$ variations, one may estimate, using Eq. 20, that $F''K_0$ increased following a slightly curvilinear function of $\dot{V}O_2$. Although $[la^-]_b$ decreased during moderate AR, lactate apparent production was multiplied by 1.45 during the 60 W AR. Because $[la^-]_b$ is the balance between production and removal, it is obvious that $[la^-]_b$ alone was not an accurate indicator of lactate production. The proportional changes of $F''K_0$ presented here is in good agreement with the values reported by Mazzeo et al. (1986) who have estimated the blood lactate disposal rate during rest and exercise using a Na^+-L (+)-[1-^{13}C] lactate intravenuous bolus injection. Indeed for steady-state exercise requiring a $\dot{V}O_2$ of 3.1 l·min^{-1}, the previous authors have found a blood lactate disposal rate 2.56 fold greater than at rest whereas in the present study, the most intense AR required a $\dot{V}O_2$ of 2.80 (SEM 0.16) l·min^{-1} and the apparent lactate production was multiplied by 2.61 (SEM 0.53). The small discrepancy between the proportional results of the two studies is the form of the relationship between lactate production and $\dot{V}O_2$. Based on three $\dot{V}O_2$ levels, the results presented by Mazzeo et al. (1986) have shown a linear relationship between the blood lactate disposal rate and $\dot{V}O_2$ whereas our results (six $\dot{V}O_2$ levels) showed that $F''K_0$ is a slightly curvilinear function of $\dot{V}O_2$ (Fig. 4). It seems thus that lactate production is almost directly related to the metabolic rate.

Changes in $F''K_0$ ratio yields an estimation of the proportional increase of apparent lactate production during AR in comparison with PR. To estimate quantitatively lactate production, the R_{bl} would be calculated using Eq. 22. However, because of the lack of data concerning V_d and its potential changes during exercise, R_{bl} is presented related to V_d. During PR, the $R_{bl} \cdot V_d^{-1}$ mean value is 85.90 (SEM 14.43) µmol·min^{-1}·l^{-1}. As the turnover values are usually reported related to the body mass, to compare our results with others previously published, the size of V_d must be assumed, – which should be done with caution! Thus, assuming that V_d during the steady state is the total body water (67% of the body mass), the value of R_{bl} during PR reported here (57.55 µmol·min^{-1}·kg^{-1}) is greater than has been presented at rest in humans by Searle and Cavalieri (1972; 17.59 µmol·min^{-1}·kg^{-1}) and by Mazzeo et al. (1986; 22.85 µmol·min^{-1}·kg^{-1}). Other authors have estimated the lactate turnover in resting humans using the Steele's nonsteady-state equations. They have reported turnover values of 14 µmol·min^{-1}·kg^{-1} (Stanley et al. 1985) and 60 µmol·min^{-1}·kg^{-1} (McRae et al. 1992), respectively. On the other hand, using ^{3}H- and ^{14}C-labelled lactate, Okajima et al. (1981) have found in starved rats a lactate turnover value of 88.9 µmol·min^{-1}·kg^{-1}.

It seems thus that large discrepancies exist between absolute values of R_{bl} reported by various investigators. These differences may come from three major sources:

1. In our experiment, StrEx could have influenced the postexercise R_{bl}.
2. Different values could be attributed to V_d.
3. Different tracers have been used. Infusion of carbon labelled molecules goes with isotopic carbon recycling (reversible tracers) which tends to underestimate the true R_{bl}. The use of hydrogen labelled molecules escapes to this recycling phenomenon (irreversible tracers) but protons are widely exchanged with their environment and tend therefore to overestimate the true R_{bl}.
4. Different types of infusion-sampling have been used. Several authors have compared, theoretically as well as experimentally, the methods of arterial infusion and venuous sampling (a-v mode) with venous infusion and arterial (or arterialized) sampling (v-a mode), particularly because the specific activity of lactate has depended on where the tracer is infused or injected and where the blood is sampled (for reviews see Katz 1992; Sacca et al. 1992). It seems that the a-v mode estimate of R_{bl} has allowed values 25%–50% greater than the v-a mode estimate.

The results of the present study avoid these criticisms. The use of endogeneous lactate to estimate R_{bl} is in perfect agreement with the natural pathways of lactate metabolism. Indeed after StrEx, lactate appears first in the muscles and then in the blood whereas after infusion, the lactate tracer appears first in the blood and then penetrates into the muscles according to kinetics which are not the same as the kinetics of the lactate release from the muscles.

Changes in $F''K_0$ during recovery have been calculated independently of V_d which has been assumed to

be constant and R_{bl} has been presented related to $\dot{V}_d$. In addition, the model does not require labelled molecules and yields quantitative changes of R_{bl}. However, as the disappearance rate constant has been shown to be dependent on the intensity of the previous exercise (Freund et al. 1986), the R_{bl} reported here should not be extrapolated to other exercise situations.

Similarly to $F''K_0$, $R_{bl} \cdot \dot{V}_d^{-1}$ increased during exercise following a slightly curvilinear function of $\dot{V}O_2$ (Fig. 5). As, has previously been shown by Stanley et al. (1988), very important inter-individual differences were observed for $R_{bl} \cdot \dot{V}_d^{-1}$ which reached 314.09 (SEM 153.95) $\mu mol \cdot min^{-1} \cdot l^{-1}$ during the most strenuous exercise (180 W).

In summary, a kinetic model which does not require labelled molecules has been presented. This model makes it possible to follow the proportional change of apparent lactate clearance and apparent lactate production during several levels of exercise in comparison with rest. Moreover, R_{bl} can also be calculated independently of the use of a tracer.

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