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Simple kinetic model for the study of lactate metabolic adaptation to exercise in sportsmen routine evaluation

BY

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(3 figures)

The interindividual specific lactate metabolic adaptation to exercise has been studied. A simple kinetic model was used which did not require labelled molecules. An one open compartment model with a first- order release rate constant described the release of lactate from the muscle. Six volunteers performed five times the same session : pedaling as long as possible at 400 W and 110 rpm. The lactate concentration was measured along the 60 min of recovery. The theoretical curve corresponding to the model was fitted to the experimental data using a non-linear regression method. The values of the following kinetic parameters were obtained : elimination rate constant (*ke*), release rate constant (*ka*), apparent amount released into the compartment divided by the volume of distribution (*FQo/Vd*) and area under the lactate concentration-time curve (AUC). Two way-ANOVA, Scheffé test and discriminant analysis were used to test the statistical significance of these parameters. No significant intra-individual variations were shown. Significant differences were observed between subjects ($ke : P = 0.0020$; $ka : P < 0.0001$; $FQo/Vd : P = 0.0002$; $AUC : P = 0.0395$). A correlation was also found between *FQo/Vd* and *ke* ($r = 0.72$; $P < 0.001$). In conclusion, the computed parameters provided by the model are sufficient to discriminate and characterize the metabolic response of each subject after short and intensive exercises.

Introduction

Blood maximum lactate level is usually used to evaluate the intensity of anaerobic metabolism during an intensive exercise (De Bruyn & Sturbois, 1978). Donovan & Brooks (1983) suggested that endurance training does not affect lactate production but lactate elimination. The decrease of lactate peak would be the reflect of an increased lactate clearance. Mazzeo *et al.* (1986) used the stable non-radioactive [1-^{13}C]-lactate to assess the metabolic fate of lactate. They concluded that the metabolic clearance of lactate increases in the transition from rest to light exercise and decreases during heavy exercise. Moreover, blood lactate irreversible disposal rate is directly related to oxygen uptake ($\dot{V}O_2$). Thus, blood lactate concentration alone is not an accurate indicator for lactate production (Eldridge, 1974; Eldridge,

1975; Katz *et al.*, 1981; KATZ, 1986; MINAIRE *et al.*, 1971). As tracers methods are not suitable for routine evaluation of sportsman, mathematical models were used to explain exchange flux of lactate between the body compartments. Two open compartment models were used (FREUND & GENDRY, 1978; FREUND & ZOULOUMIAN, 1981a & b; ZOULOUMIAN & FREUND, 1981a & b). In such models, quantification of some parameters like central and peripheral volumes of distribution, are impossible on a theoretical bases due to the lactate elimination from the peripheral compartment (COUET, 1986).

The present study develops a one open compartment model with a first order release rate constant (GIBALDI & PERRIER, 1982) for lactate kinetics leading to usefull parameters for routine characterization of the lactate metabolic adaptation to exercise. The usefulness of the model was tested by a discriminant analysis comparing the kinetic parameters profile of six volunteers.

Methods and Materials

Subjects

Six male students in physical education served as subjects for this study. All men were volunteers, in good physical condition and practicing regularly sports. The biometric data of the subjects are presented in Table I.

TABLE I. *Biometric data of the subjects.*

Subjects	Age (years)	Height (cm)	Weight (kg)
1	20	175	64
2	20	172	69
3	22	172	76
4	23	184	79
5	23	181	71
6	24	182	73

Materials

The exercise sessions were performed on a bicycle ergometer *(*380B, *Siemens, Elema).*

The blood lactate concentrations were analysed using a classical enzymatic procedure *(Boehringer-Mannheim).*

Model

A. Equations describing the lactate concentration at rest.

The lactate concentration at rest corresponds to an equilibrium between its production and its elimination. This can be represented by the following equation :

$$\frac{dQ}{dt} = ko - ke \cdot Q \qquad (1)$$

where : ko is a zero constant which describes the constant production of lactate at rest,
ke is a first order rate constant which describes the elimination of lactate from the blood compartment,
Q is the lactate amount in the body,

After integration, equation 1 becomes :

$$Qt = \frac{ko}{ke} \cdot (1 - e^{-ke.t}) \quad (2)$$

where Qt is the lactate amount in the body at time t.

Since the lactate production has been started for a long time, t is equal to infinity. Therefore, equation 2 becomes :

$$Qss = \frac{Ko}{ke} \quad (3)$$

where Qss is the lactate amount in the body at the steady state.

If one assumes there exists a constant relationship between lactate in the blood *(C)* and the amount of lactate in the body *(Q)* :

$$Q = C \cdot Vd \quad (4)$$

where Vd is the volume of distribution of lactate.

The relationship between the lactate blood concentration and the amount of lactate in the body as expressed by equation (4) enables the conversion of equation (3) from an amount-time to concentration-time which may be expressed as :

$$\frac{Qss}{Vd} = Css = \frac{Ko}{ke \cdot Vd} \quad (5)$$

where Css is the blood lactate concentration at the steady state.

B. Equations describing lactate concentration after a short and intensive exercise

At the end of a short and intensive exercise, the blood lactate concentration increases during the first few minutes of recovery to reach a peak. Then it decreases following an exponential function *vs.* time.

This figure corresponds to the production and the release of lactate from the muscle into the blood and its elimination from the blood.

This phenomenon may be represented by the following equation :

$$\frac{dQ}{dt} = ka \cdot Qo - ke \cdot Q \quad (6)$$

where ka is a first- order rate constant which accounts for the release of lactate into the blood compartment.
Qo is the amount of lactate produced during the exercise.

After integration, equation (6) becomes :

$$Qt = Qo \cdot \frac{ka}{ka - ke} \cdot (e^{-ke.t} - e^{-ka.t}) \quad (7)$$

Considering equation (4), the lactate concentration due to the short and intensive exercise may be described by the following equation

$$Ct = \frac{Qo}{Vd} \cdot \frac{ka}{ka - ke} \cdot (e^{-ke.t} - e^{-ka.t}) \quad (8)$$

Because all the lactate produced does not appear necessarily into the blood compartment, a proportionnality constant must be applied to equation (8) to give :

$$Ct = \frac{FQo}{Vd} \cdot \frac{ka}{ka - ke} \cdot (e^{-ke.t} - e^{-ka.t}) \quad (9)$$

where F is the fraction of lactate amount that is released into the blood.

Combining equations (5) and (9), one obtains :

$$Ct = \underbrace{\frac{FQo}{Vd} \cdot \frac{ka}{ka - ke} \cdot (e^{-ke.t} - e^{-ka.t})}_{A} + \underbrace{\frac{Ko}{ka.Ve}}_{B} \quad (10)$$

This equation describes the lactate concentration during the recovery period after a short and intensive exercise. The first member of the equation (A) accounts for the lactate kinetics corresponding to the short and intensive exercise only. The second member of the equation (B) accounts for the lactate kinetics corresponding to the rest.

Equation (10) may be also expressed :

$$CT = \frac{FQo}{Vd} \cdot \frac{ka}{ka - ke} \cdot (e^{-ke.t} - e^{-ka.t}) + k \quad (11)$$

where k is the constant blood lactate concentration at rest.

The model described above corresponds to the one open-compartment model applied to the lactate kinetics. In such a model, the elimination rate constant *(ke)* is an apparent constant which is the ratio between the clearance *(Cl)* and the volume of distribution *(Vd)*.

$$ke = Cl / Vd \quad (12)$$

Integration of equation (9) from zero to infinity yields :

$$\int_{t=0}^{t=\infty} C\,dt = \frac{FQo}{Vd} \cdot \frac{ka}{ka - ke} \cdot \left(\frac{1}{ke} - \frac{1}{ka}\right) = AUC \quad (13)$$

This equation gives the area under the lactate concentration-time curve (AUC) due to the short and intensive exercise only.

Rearrangement of equation (13) yields :

$$AUC = \frac{FQo}{Vd \,.\, ke} = \frac{FQo}{Cl} \qquad (14)$$

Experimentation

The exercise sessions consisted of a short and intensive exercise. The subjects began to pedal at 110 rpm at a workload of 80 W. This very easy workload allowed to reach the stipulated rythm in a few seconds. After five seconds, the workload was put up to 400 W. The session was stopped abruptly when the subject could not pedal at 80 rpm any more. The durations of the sessions are given in Table II. Before the session a catheter was introduced in the antecubital vein of the subjects. Blood samples were taken prior to and immediately following the exercise at 1st, 2nd, 3rd, 5th, 6th, 8th, 10th, 12th, 15th, 20th, 25th, 30th, 40th, 50th and 60th minute. Each subject performed five times the same session at five different days. The blood lactate determinations were performed after each session following the same procedure.

TABLE II. *Mean ($\bar{x}$) and standard deviation (s) of the duration of the exercise (400W, 110rpm), elimination rate constant (ke), release rate constant (ka), lactate fraction released into the blood compartment divided by the volume of distribution (FQo/Vd) and area under the lactate concentration-time curve (AUC) observed in six subjects which performed five times the same short and intensive exercise (400W, 110rpm).*

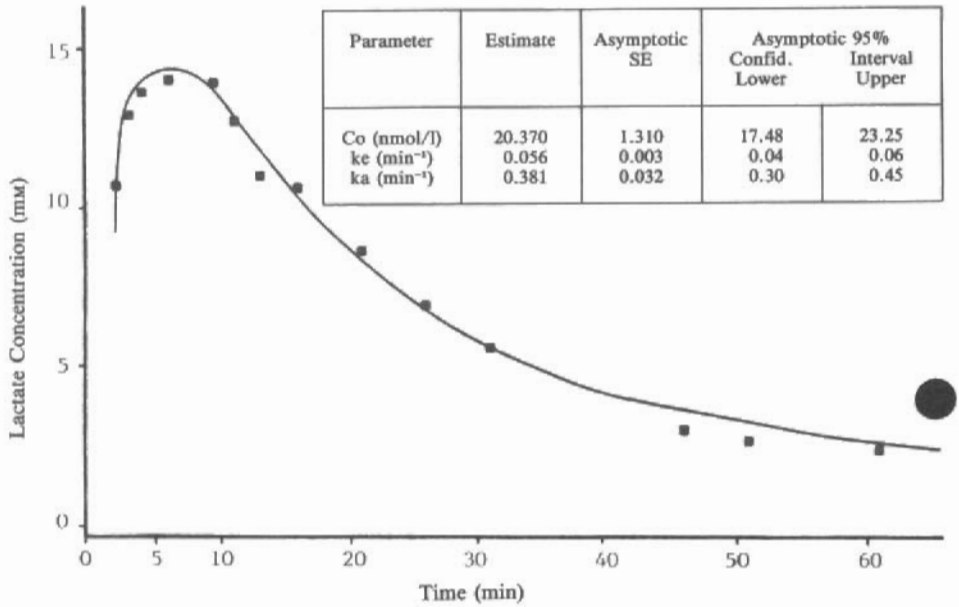
Subjects	duration (s)		*ke* (min^{-1})		*ka* (min^{-1})		*FQo/Vd* (mmol $litre^{-1}$)		AUC (min.mmol $/litre^{-1}$)	
	$\bar{x}$	s	$\bar{x}$	s	$\bar{x}$	s	$\bar{x}$	s	$\bar{x}$	s
1	73.6	3.13	0.061	0.0059	0.348	0.035	16.61	1.01	316.66	26.82
2	64.8	6.87	0.053	0.0047	0.254	0.090	15.40	1.14	288.32	66.68
3	62.4	3.56	0.053	0.0154	0.132	0.029	18.94	2.77	369.54	36.05
4	95.2	11.99	0.038	0.0102	0.267	0.054	11.76	1.18	312.48	60.96
5	81.8	5.54	0.076	0.0151	0.169	0.040	19.08	2.51	253.45	31.82
6	82.6	6.58	0.072	0.0179	0.120	0.039	19.46	1.70	284.86	63.75

Statistical analyses

All statistical analyses were computed by SAS (1985). The lactate kinetic have been computed in accordance with the model presented above and following the DUD non-linear regression method. Two way-ANOVA, Scheffé test, correlation and discriminant analysis were used to test the statistical significance of the variability due to the sessions and due to the subjects.

Results

Fitting the theoretical function to the data gives satisfactory results. Figure 1 presents a typical function as found during experimentation. Parameter estimate, asymptotic standard error and asymptotic 95% confidence interval are also presented.



Parameter	Estimate	Asymptotic SE	Asymptotic 95% Confid. Interval Lower	Upper
Co (nmol/l)	20.370	1.310	17.48	23.25
ke (min^{-1})	0.056	0.003	0.04	0.06
ka (min^{-1})	0.381	0.032	0.30	0.45

FIGURE 1. *Blood lactate concentration after a short and intensive exercise* (400W, 110rpm) *in a healthy volunteer.* Inset : Parameters estimate, asymptotic standard error and asymptotic 95% confidence interval. *Co* = (*FQo*/*Vd*). (*ka*/*ka*-*ke*)

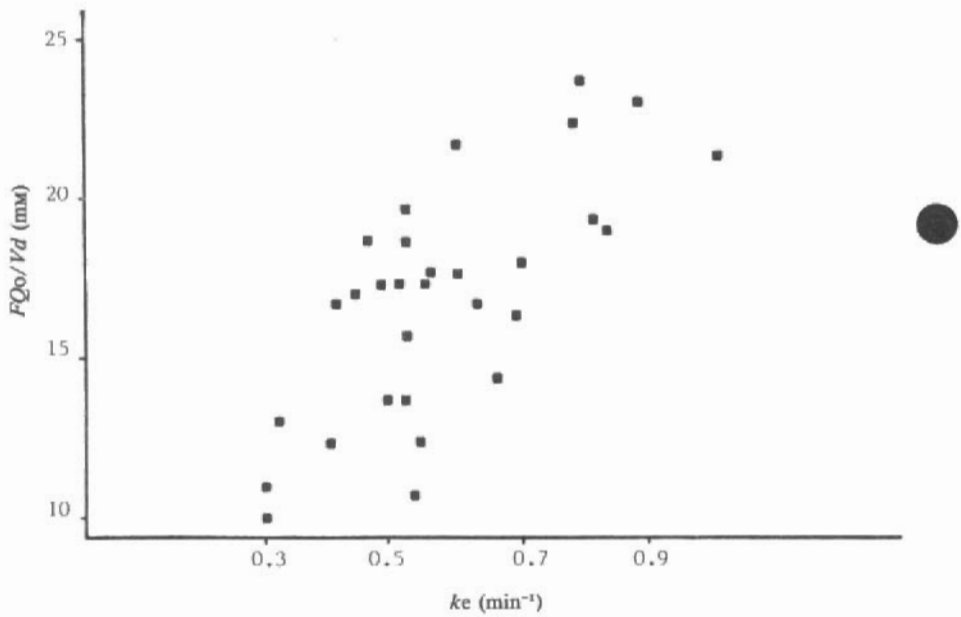


FIGURE 2. *Relationship between* ke (C1/Vd) *and* FQo/Vd) *obtained in six subjects which performed five times the same short and intensive exercise (400W, 110 rpm).*

All lactate kinetics were computed according to the model presented above. The means and the standard deviations of *k*e, *k*a, *FQ*o/*V*d and AUC are presented for each subject in Table II.

The highest mean value of *k*e is 0.076/min corresponding to a half-live of 9.16 min and the lowest mean value is 0.038/min corresponding to a half-live of 18.23 min.

Two way-ANOVA applied to *k*e data shows a significant difference between the subjects ($P = 0.0020$). No difference is observed between the experiences.

*K*a is the release rate constant. Its mean varies between 0.120/min and 0.348/min. Two way-anova shows a significant difference between the subjects ($P<0.001$) and no difference between experiences.

*FQ*o/*V*d is the fraction of the produced lactate amount released into the compartment divided by the volume of distribution *(V*d*)*. The highest mean value of *FQ*o/*V*d is 19.46 mM and the lowest is 11.76 mM. Two way-ANOVA shows a significant difference between the subjects ($P=0.0002$) and no difference between experiences.

Moreover, corelation is observed between *FQ*o/*V*d and *k*e ($r=0.72$; $P<0.0001$) (Fig. 2).

The highest mean value of AUC is 369.54 mM and the lowest is 253.45 mM. ANOVA shows a significant difference between subjects AUC ($P=0.0395$).

Then, *k*e, *k*a and *FQ*o/*V*d data were submitted to the discriminant analysis. As each subject performed five times the same session, the discriminant analysis should put together the five profiles of the same subject. This analysis has correctly classified 22 profiles on 30 (73.33% well-classified) (Table III).

TABLE III. *Discriminant analysis realized on* ke, ka *and* FQo/Vd *in six subjects which performed five times the same short and intensive exercise* (400W, 110rpm).

From subject	Number of observations and percents classified into subject						
	1	2	3	4	5	6	TOTAL
1	4	1	0	0	0	0	5
	80	20	0	0	0	0	100
2	1	3	1	0	0	0	5
	20	60	20	0	0	0	100
3	0	0	4	0	0	1	5
	0	0	80	0	0	20	100
4	0	0	0	5	0	0	5
	0	0	0	100	0	0	100
5	0	0	0	0	3	2	5
	0	0	0	0	60	40	100
6	0	0	2	0	0	3	5
	0	0	40	0	0	60	100
TOTAL	5	4	7	5	3	6	30
	17	13	23	17	10	20	100

Discussion

The pattern of the observed lactate curve after a short and intensive exercise is in good agreement with other studies examining lactate kinetic in human after exercise (BELCASTRO & BONEN, 1975; DI PRAMPERO *et al.*, 1978; FREUND & GENDRY, 1978). After the end of the exercise, the blood lactate concentration increases during the first few minutes of recovery to reach a peak. Then, it decreases following an exponential function *vs.* time. The kinetic analysis of this blood lactate concentration profile based on the one open-compartment model leads to kinetic parameters : elimination rate constant *(ke)*, release rate constant *(ka)*, apparent amount released into the compartment divided by the volume of distribution *(FQo/Vd)* and area under the lactate concentration-time curve (AUC).

Kinetic parameters and their discriminant capability

All the parameters provided by the model are apparent. They integrate several physiologic phenomena.

1. The lactate fraction released into the compartment divided by the volume of distribution (*FQo/Vd*)

The body is obviously not homogeneous even if blood lactate concentration data can be described by representing the body as a one-compartment model. Lactate concentrations in the liver, kidneys, heart, muscle and other tissues will usually differ from one another as well as from the concentration in the blood. If the relative lactate concentration of these tissues and fluids is essentially independent of lactate concentration, then the ratio of lactate concentrations in various tissues and fluids is constant. Consequently, there will exist a constant relationship between lactate concentration in the blood and the amount of lactate in the body at steady state. The proportionality constant that describes this relationship is known as the apparent volume of distribution. Despite its name, this constant, usually used, has no direct physiological meaning and does not refer to a real volume. Several authors have estimated this apparent volume of distribution (AHLBORG *et al.*, 1976; FREUND & GENDRY, 1978; SEARLE & CAVALIERI, 1972; STURBOIS & JACQMIN, 1983).

FQo represents the lactate fraction released into the compartment divided by the volume of distribution. Contrary to the lactate peak (*Cmax*), *FQo/Vd* represents an apparent parameter which is not inflected by elimination (*ke*) and release (*ka*) phenomena.

Indeed, *Cmax* corresponds to :

$$Cmax = \frac{FQo}{Vd}\,\frac{ka}{ka\text{-}ke}\left(e^{-ke\,\frac{1}{ka\text{-}ke}\,ln\,\frac{ka}{ke}} - e^{-ka\,\frac{1}{ka\text{-}ke}\,ln\,\frac{ka}{ke}}\right) + K$$

FQo/Vd is greatly discriminant. Nevertheless, taking into consideration the wide range of variations of *FQo/Vd* and the high homogeneity of the biometric parameters of our population (Table 1), *FQo/Vd* variations between subjects could be interpreted more as *FQo* variations than *Vd* variations.

The correlation found between *FQo/Vd* and *ke (Cl/Vd)* ($r = 0.72$; $P < 0.0001$) could be due to the variations of the volume of distribution, *FQo* and *Cl* remaining constant in all subjects. But, because of the wide range of variations, this correlation

could express the fact that the more subjects produce lactate, the more their clearance is high.

Indeed, MAZZEO *et al.* (1986), report that for the same individual the metabolic clearance increases with the intensity of the exercise to reach a peak. Afterwards it decreases (this decreasing is probably due to a saturation of disposal processes because of the intensity of the exercise (above the lactate threshold). Therefore, the correlation found between FQo/Vd and ke obtained for different individuals in our experimental conditions suggests that the intra-individual observation made by MAZZEO *et al.* (1986), could be extended and that in a population, a relationship exists between the capability to produce a determined lactate amount and the disposal rate. The main source of lactate production is also the main site of its elimination : the muscle.

2. The elimination rate constant (ke).

Without tracers, Cl and Vd cannot be separately quantified experimentally because the lactate amount present in the body is not known. Their ratio may be estimated by the elimination rate constant ($ke = Cl/Vd$). In our experiment, ke was different for each subject. Therefore Cl or/and Vd could be considered as discriminant. But, as for FQo/Vd the wide range of variations seems to indicate that Cl is the main factor.

In fact, the decreasing phase in the blood lactate concentration profile is the reflection of lactate elimination by different processes (MINAIRE, 1973) : renal clearance, cardiac clearance, hepatic clearance, muscular clearance,... Each clearance corresponds to the blood flow through the elimination organ multiplied by the extraction coefficient of this organ. Now, it is well known that during an exercise the systolic debt is greatly increased. Moreover there exists a great controversy about the major fate of lactate disposal (BROOKS *et al.*, 1973; ISSEKUTZ *et al.*, 1976; HERMANSEN & VAAGE, 1977; BROOKS & GAESSER, 1980; GAESSER & BROOKS, 1980; BROOKS, 1986) and it is accepted that the metabolism rate varies in function of the level of the exercise. These variations of the blood flow and the extraction coefficient could be different for each subject and could explain the specific adaptation of each individual to eliminate lactate and the discriminant capability of the elimination rate constant.

Moreover, during standardized conditions, it seems that the lactate clearance may be apparently assimilated to a constant for each subject. In our experiment, after the short and intensive exercise, the subjects stopped the muscular activity and the energetic demand decreased rapidly. The lactate production also decreased and the lactate disposal processes became not saturated leading to a normal and apparent constant lactate clearance. The linear decrease of the logarithm of the lactate concentrations *vs.* time during the elimination phase accounts for this apparent constant clearance (Fig. 3).

3. The area under the lactate concentration-time curve (AUC).

AUC is equal to the lactate amount released into the compartment divided by the clearance ($AUC = FQo/Cl$). AUC is independent of the volume of distribution. Two way-ANOVA applied to AUC data, shows a significant difference between the AUC of the subjects ($P = 0.0395$). Nevertheless, the Scheffé test does not confirm this difference and ANOVA applied on the whole statistical model (subjects plus experiments) does not show significant difference. These results may be explained by the fact that FQo and Cl vary in the same way as shown by the results in Figure 2.

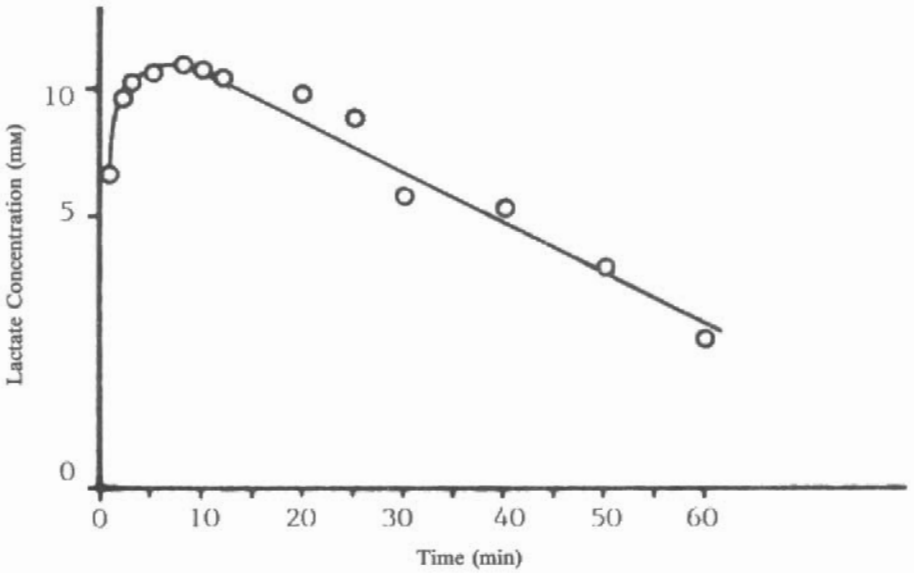


FIG. 3. *Evolution of blood lactate concentration corresponding to the exercise only,* vs. *time.* The blood lactate concentrations corresponding to the exercise only were obtained after subtraction of the rest lactate concentration from the observed lactate concentrations.

This observation confirms the hypothesis that the more an individual is able to produce lactate (*FQ*o) the more its clearance is high.

4. The release rate constant (*k*a).

This parameter differs from one another individual ($P<0.0001$) and thus is very discriminant. Nevertheless, few observations are available for the discussion of *k*a signification. Muscles release lactate through the surface membrane by three mechanisms : ionic (A), proton linked (B) and undissociated acid (C) (MAINWOOD *et al.*, 1987). MASON & THOMAS (1988) concludes that lactate crosses the membrane of the frog sartorius muscle *via* (1) a carrier-mediated process and (2) passive diffusion of lactic acid. In the physiological range of lactate concentrations and pH the transport processes dominate. Nevertheless, no saturation is observed at lactate concentration between 5 and 60 mM at pH 7.35. In our experimental conditions, the lactate release followed apparently a first-order kinetic.

Kinetic model : discriminant capability and reliability

Two way-ANOVA applied to *FQ*o/*Vd*, *k*e and *k*a shows for each parameter a significant difference between subjects but not between sessions. This suggested the specific lactate metabolic adaptation of each subject. To verify the good reliability and the discriminant character of the model, the data of *FQ*o/*Vd*, *k*e and *k*a were submitted to the discriminant analysis. This analysis classified correctly 22 profiles on 30 (73.33%

well-classified) (Table III). These results demonstrate the good reliability and the discriminant character of the model which can thus be used for the characterization of the lactate metabolic adaptation to exercise in routine sportsmen evaluation.

In conclusion :

1) the present study has submitted a simple kinetic model leading to parameters which integrate several physiologic phenomena.
2) these kinetic parameters are sufficient to discriminate and characterize the metabolic response of each individual after a short and intensive exercise.
3) the basis of this discriminant character is partially due to the relationship between the capability to produce a determined lactate amount and to eliminate it.
4) our model confirms that the maximum blood lactate concentration alone is not an accurate indicator of the lactate production during exercise.
5) the model is easy to apply for routine evaluation of sportsmen.

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