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Blood lactate exchange and removal abilities after relative high-intensity exercise: effects of training in normoxia and hypoxia

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Abstract The effects of 4 weeks of endurance training in conditions of normoxia or hypoxia on muscle characteristics and blood lactate responses after a 5-min constant-load exercise (CLE) at 90% of the power corresponding to the maximal oxygen uptake were examined at sea-level in 13 sedentary subjects. Five subjects trained in normobaric hypoxia (HT group, fraction of oxygen in inspired gas = 13.2%), and eight subjects trained in normoxia at the same relative work rates (NT group). The blood lactate recovery curves from the CLE were fitted to a biexponential time function:

$La_{(t)} = La_{(0)} + A_1(1 - e^{-\gamma_1 \cdot t}) + A_2(1 - e^{-\gamma_2 \cdot t})$, where the velocity constants γ_1 and γ_2 denote the lactate exchange and removal abilities, respectively, A_1 and A_2 are concentration parameters that describe the amplitudes of concentration variations in the space represented by the arterial blood, $La_{(t)}$ is the lactate concentration at time t , and $La_{(0)}$ is the lactate concentration at the beginning of recovery from CLE. Before training, the two groups displayed the same muscle characteristics, blood lactate kinetics after CLE, and γ_1 and γ_2 values. Training modified their muscle characteristics, blood lactate kinetics and the parameters of the fits in the same direction, and proportions among the HT and the NT subjects. Endurance training increased significantly the capillary density (by 31%), citrate synthase activity (by 48%) and H isozyme proportion of lactate dehydrogenase (by 24%), and γ_1 (by 68%) and γ_2 (by 47%) values. It was concluded that (1) endurance training improves the lactate exchange and removal abilities estimated during recovery from exercises performed at the same relative work rate, and (2) training in normobaric hypoxia results in similar effects on lactate exchange and removal abilities to training in normoxia performed at the same relative work rates. These results, which were obtained non-invasively in vivo in humans during recovery from CLE, are comparable to those obtained in vitro or by invasive methods during exercise and subsequent recovery.

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Introduction

It has been shown that capillarization (Tesch and Wright 1983) and carrier-mediated lactate transport (Juel 1997), which are two of the determining factors of lactate release from exercising muscles to the blood, are significantly improved by training (Ingjer 1979;

Pilegaard et al. 1999; Dubouchaud et al. 2000). However, the effects of training on the lactate exchange processes between the active muscles and the blood deserve further *in vivo* exploration in humans. From a conceptual point of view, it can reasonably be assumed that after high-intensity muscular exercises, the net lactate release rate from the muscles involved in the exercise to the blood depends not only on the lactate gradient, but also on the efficiency with which lactate is released. The velocity constants γ_1 and γ_2 of the biexponential time function fitted to the arterial lactate recovery curves obtained after muscular exercise have been shown to supply information on the lactate exchange ability between the previously active muscles and the blood (γ_1) as well as on the body's overall ability to remove lactate (γ_2) during the recovery (Freund et al. 1986; Freund and Zouloumian 1981). So far, this approach has not been applied in a longitudinal study that has been designed to investigate the effect of training on lactate exchange ability.

Studies on the influence of training on the lactate removal processes have provided differing results. According to Bassett et al. (1991), the training affects neither the pattern of blood lactate decline nor the lactate removal ability (γ_2) during recovery after 3 min of exercise at $\cong 85\%$ of maximum oxygen uptake ($\dot{V}O_{2\max}$). These results conflict with those obtained by MacRae et al. (1992), whose study involved the use of tracers during exercise. Specifically, these authors observed, during incremental exercises (IE) leading to $\cong 75\%$ of $\dot{V}O_{2\max}$, lower blood lactate concentrations after 9 weeks of endurance training, and attributed this decrease to the training-induced elevation of the lactate metabolic clearance rate (MCR). The results of Bassett et al. (1991) also contrast with a recent study of Messonnier et al. (1997), who found a positive correlation among high level oarsmen between the relative work rate corresponding to the 4 mmol·l⁻¹ blood lactate concentration obtained during an IE (anaerobic threshold) and the recovery lactate removal ability. In view of these opposing results, the effect of training on the lactate removal ability during recovery from high-intensity exercises performed at the same relative work rate before and after training deserves to be re-examined.

A number of coaches and athletes remain convinced that moderate-altitude training is more effective than normoxic training for improving the physical aptitude at sea level. Previous studies have already investigated the effects of acute and chronic hypoxia on lactate kinetics (Brooks et al. 1992, 1998). However, no study has compared the effects of training in hypoxia and in normoxia on the sea-level lactate exchange and removal abilities. If the potentiating effect of hypoxia during training on the lactate exchange and removal abilities can be proved, the information would be of interest for the coaches of athletes involved in endurance events. Indeed, it has been shown that the better performance during a 2500-m all-out rowing test lasting for more

than 7.5 min is associated with better lactate exchange and removal abilities (Messonnier et al. 1997).

Thus, we performed experiments in a population of sedentary subjects to compare the effects of 4 weeks of endurance training, conducted at the same relative work rates in conditions of normoxia and in normobaric hypoxia, on the sea-level lactate exchange and removal abilities during recovery from muscular exercise. In view of the paucity of data on the *in vivo* lactate exchange ability in humans and the conflicting results obtained by previous authors for lactate removal, another aim was to examine whether endurance training would improve these dynamic parameters during recovery from short-duration, high-intensity exercises performed at the same relative work rate before and after training.

Methods

Subjects

Thirteen healthy subjects (three females and ten males) participated in the study. Their mean (SE) age, body mass and height were 20.5 (0.5) years, 70 (5) kg and 175 (3) cm, respectively. Before giving their written consent to participate, they were informed of the nature, the potential risks involved and the benefits of the study. The experiments received the approval of the Ethical Committee on Human Research of the institution involved, at Saint-Etienne.

Experimental design

Two weeks before the start of the experiments, all of the subjects were submitted to an inclusion protocol. This consisted of a physical examination, anthropometric measurements and an IE up to exhaustion that allowed the subjects to become accustomed to the equipment and testing procedures. All of the exercise tests were performed in the upright position using a bicycle ergometer (Monark 818E, Stockholm, Sweden). The instantaneous power output and the pedaling frequency (set at 75 rpm) were delivered on-line by a computer device that was developed in the laboratory. The experiments and training sessions were conducted either in normoxia (inspired partial pressure of oxygen, $P_{iO_2} = 141$ mmHg, 18.8 kPa) or in normobaric hypoxia ($P_{iO_2} = 89$ mmHg, 11.9 kPa). The protocol consisted of pre-training, training and post-training periods.

Pre-training period

This involved three experimental sessions separated by at least 2 days.

Session 1: IE test up to exhaustion in normoxia

The test began with a 2-min rest period on the ergometer, followed by 2 min of warm-up cycling at 0 W. The work rate was then set at 60 W for the men and 40 W for the women. After 2 min of cycling at this load, the work rate was incremented every 2 min by 30 W for the males and 20 W for the females. This procedure was continued until exhaustion, which was defined as the point at which the subjects could no longer maintain the requested pedaling frequency. Expired gas samples were analyzed continuously for oxygen uptake ($\dot{V}O_2$) measurement. Capillary blood samples were collected from the fingertip prior to the exercise and during the last 20 s of each exercise step, for the determination of the arterialized blood lactate concentration. This session was carried out to estimate the maximal oxygen uptake ($\dot{V}O_{2\max}$, l·min⁻¹), the corre-

sponding maximal aerobic power ($\dot{W}_{\text{aer,max}}$, $\text{W}\cdot\text{kg}^{-1}$), the work rates corresponding to 60, 70, 80 and 90% of $\dot{W}_{\text{aer,max}}$ and the $\dot{V}\text{O}_2$ corresponding to the 4 $\text{mmol}\cdot\text{l}^{-1}$ blood lactate concentration, expressed as percentage of $\dot{V}\text{O}_{2\text{max}}$ (AT4%).

Session 2: IE test up to exhaustion in normobaric hypoxia

Except for the work rate at the first step and the breathing gas conditions, the subjects performed the same protocol as in session 1. The IE started at 40 W for the males and 20 W for the females. To simulate altitude, hypoxia was realized by a reduction to 13.2% of the inspired oxygen fraction. This induced a fall of the $P_{\text{I}}\text{O}_2$ to a value equivalent to that at 3800 m. This session was carried out to determine the peak oxygen uptake ($\dot{V}\text{O}_{2\text{peak}}$, $\text{l}\cdot\text{min}^{-1}$) in hypoxia, the corresponding peak aerobic power ($\dot{W}_{\text{aer,peak}}$, $\text{W}\cdot\text{kg}^{-1}$), and the power corresponding to 60, 70 and 80% of $\dot{W}_{\text{aer,peak}}$.

Session 3: Constant-load exercise test

The subjects received a light standard breakfast 90 min prior to the test. A hyperemic cold cream (Dolpyc) was applied to the earlobe 10 min before the onset of the exercise test to arterialize the blood. The test began with a warm-up exercise (30–40% $\dot{W}_{\text{aer,max}}$ for 3 min), which was immediately followed by a 5-min period of exercise at 90% $\dot{W}_{\text{aer,max}}$ and a subsequent passive recovery period of 90 min. Blood samples were collected from the earlobe at the end of exercise, and at minutes 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 85 and 90 of the recovery. This session served to assess the individual blood lactate recovery parameters.

Training period

The training schedule consisted of pedaling on the ergometer for 2 $\text{h}\cdot\text{day}^{-1}$, 6 $\text{days}\cdot\text{week}^{-1}$, for 4 weeks. All of the subjects trained at the same relative work rate, but at two different partial pressures of oxygen. One group (HT) of five subjects (four males and one female: SH1–SH5) trained in normobaric hypoxia, while the other group (NT) of eight subjects (six males and two females: S1–S8) trained in normoxia. The relative work rate was set at 60–70%, 70–80% and 80% of the pre-training $\dot{W}_{\text{aer,peak}}$ or $\dot{W}_{\text{aer,max}}$ (for HT and NT, respectively) for the 1st, 2nd and last 2 weeks of training, respectively. The subjects were asked to communicate the work rate and heart rate displayed on the ergometer every 10 min while exercising as a check of the experimental conditions and for comparison between training regimens.

Post-training period

To assess the metabolic adaptations induced by training, the subjects were subjected to the same experimental sessions as during the pre-training protocol. They performed the graded exercise up to exhaustion in normoxia and in normobaric hypoxia. Blood was sampled at the end of each exercise increment. At least 2 days later, they were subjected to the constant-load exercise (CLE) test, for which the work rate was set individually at 90% of the post-training $\dot{W}_{\text{aer,max}}$. Blood was again sampled at the end of exercise and, as before, during the subsequent recovery.

Measurements

Ventilation and $\dot{V}\text{O}_2$ were measured using a MedGraphics CPX/D metabolic system (St. Paul, Minn., USA). The calibration was checked after each exercise to be sure that there was no analyzer drift. When $\dot{V}\text{O}_2$ reached a plateau while the work rate was still increasing, that $\dot{V}\text{O}_2$ was considered in normoxia as $\dot{V}\text{O}_{2\text{max}}$, and in hypoxia as $\dot{V}\text{O}_{2\text{peak}}$. To establish that $\dot{V}\text{O}_{2\text{max}}$ and $\dot{V}\text{O}_{2\text{peak}}$ had been attained when a plateau was not observed, the following criteria were used: a respiratory exchange ratio greater than 1.1, an end-

exercise lactate concentration higher than 9 $\text{mmol}\cdot\text{l}^{-1}$, and the theoretical maximal cardiac frequency approximately reached (± 10 $\text{beats}\cdot\text{min}^{-1}$).

Exercise work and heart rates were determined by linear interpolation from the work and heart rate versus $\dot{V}\text{O}_2$ curves, respectively.

Micropunctures of 20 μl of blood were taken from the fingertip (sessions 1 and 2) or the earlobe (session 3). Lactate concentrations were determined enzymatically in hemolyzed blood (Geysant et al. 1985) with an L.A. 640 Kontron lactate analyzer (Roche Bioelectronics, Hoffman-La Roche, Basel, Switzerland).

Histochemical and enzyme analysis

Prior to the pre- and post-training periods, biopsy samples of the vastus lateralis muscle were taken from the individuals at rest. Small incisions were made in the skin and fascia under local anesthesia. Biopsy samples were taken with the aid of Weil Blakesley forceps. A part of the sample was immediately frozen and stored in liquid nitrogen until analyzed for enzyme activities. The other part was mounted in Tissue-Tek II O.C.T. compound for histochemical analysis. Cryostat serial transverse sections (-20°C , 10 μm) were stained for ATP activity (ATPase) to determine the muscle fiber composition (Brooke and Kaiser 1970) and for α -amylase periodic acid Schiff (reagent) activity to enable measurement of the mean cross-sectional area of each fiber type and to calculation of the mean number of capillaries around each of them (Andersen 1975). Mean muscle fiber areas were determined by averaging the cross-sectional areas of 20 randomly selected fibers of each type from the ATPase stain reaction that had been photographically reproduced at a known magnification. The cross-sectional areas were measured planimetrically (digitalizing tablet Numonics 2200). For enzyme analysis, samples were freeze-dried, dissected free from connective tissue and blood and then powdered. The muscle powder was weighed at room temperature in a box where the hygrometry was lower than 40%. The tissue was homogenized manually at 4°C in 0.1 M phosphate buffer (pH=8.2) containing 2-mercaptoethanol (5 mM), NaF (30 mM), MgCl_2 (5 mM) and ATP (0.5 mM). This tissue suspension was immediately used to measure spectrophotometrically the activity of phosphofructokinase (PFK, Enzyme Commission (EC) 2.7.1.11) using the method of Mansour (1966). The remaining aliquot was then frozen and stored at -80°C until analyzed for the other enzymes. The activity of citrate synthase (CS, EC 4.1.3.7) was determined fluorometrically (Essen-Gustavsson and Henriksson 1984) and the activity of lactate dehydrogenase (LDH, EC 1.1.1.27) was measured spectrophotometrically (Lowry and Passonneau 1972). LDH isozymes were separated by polyacrylamide gel electrophoresis; the substrate revealed isozyme fractions that were evaluated by densitometry (Rosalki 1974). All of the enzyme activities were measured at 25°C and are expressed in $\mu\text{mol}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$ of dry muscle.

Mathematical and statistical analysis

The individual pre- and post-training lactate recovery curves were fitted to the biexponential time function:

$$\text{La}(t) = \text{La}(0) + A_1(1 - e^{-\gamma_1 t}) + A_2(1 - e^{-\gamma_2 t}) \quad (1)$$

using an iterative nonlinear regression technique. In this equation, $\text{La}(0)$ and $\text{La}(t)$ ($\text{mmol}\cdot\text{l}^{-1}$) are the lactate concentration in arterialized venous blood measured at the onset of the recovery and at a time t (min) of the recovery period, respectively. The concentration parameters A_1 and A_2 ($\text{mmol}\cdot\text{l}^{-1}$) are required to describe the amplitudes of concentration variations in the space represented by the arterial blood. The velocity constants γ_1 and γ_2 (min^{-1}) of the fitted exponential functions supply information on the ability to exchange lactate between the previously worked muscle and the blood, and on the body's overall ability to remove lactate during recovery, respectively (for further details see Freund et al. 1986; Freund and Zouloumian 1981).

Descriptive statistics are expressed as means (SE). Initially, the protocol was to compare seven subjects involved in HT to eight in NT, but two of the HT subjects could not complete the study. One of them did not tolerate the hypoxic training regimen; the other fell ill. Differences between the HT and NT groups were determined by means of the Mann-Whitney U test. Once the equality of the variances was tested, the influence of the mode of training (intergroup difference among the HT and the NT subjects) and the training-induced changes (before vs after training) were assessed by analysis of variance (factorial analysis). Differences in pre- and post-training parameters were determined by means of the Wilcoxon signed rank test. The level of statistical significance was set at $P < 0.05$.

Results

Pre-training

As reported in Table 1, there were no significant differences between HT and NT in age, height, body mass, $\dot{V}O_{2\max}$ or weight-normalized $\dot{W}_{\text{aer,max}}$ prior to undergoing the training regimen. Due to the same pre-training $\dot{W}_{\text{aer,max}}$, the absolute work rates ($\text{W}\cdot\text{kg}^{-1}$) of the 5-min exercise at 90% $\dot{W}_{\text{aer,max}}$ were not different between the two groups before training. Both the average blood lactate concentrations during IE (Fig. 1A) and during recovery from CLE (Fig. 2A) did not differ significantly among the HT and NT before training. Eq. 1 fitted accurately the individual lactate recovery curves. The fits accounted for more than 98% of the data variance. As shown in Tables 2 and 3, there were no significant differences either in the parameters of the fits or in the metabolic and histochemical muscle characteristics, respectively, between HT and NT before training.

Training conditions

HT and NT performed the same training schedule in terms of relative work rate. Average heart rates measured during training were not different between HT and NT (Table 4). In terms of absolute values, HT trained at lower exercise power outputs (by 15–29%) than NT (Table 4).

Influence of the partial pressure of oxygen during training on the measured parameters

Training-induced improvements of $\dot{W}_{\text{aer,max}}$ did not differ from one oxygen partial pressure training condition to another (17.4% for HT and 16.9% for NT), so that the

Table 1 Mean values of some anthropometric, physiological and mechanical parameters. Values are presented as the means (SE). ($\dot{V}O_{2\max}$ maximal oxygen uptake, $\dot{W}_{\text{aer,max}}$ maximal aerobic power – work rate corresponding to $\dot{V}O_{2\max}$, HT group of subjects who

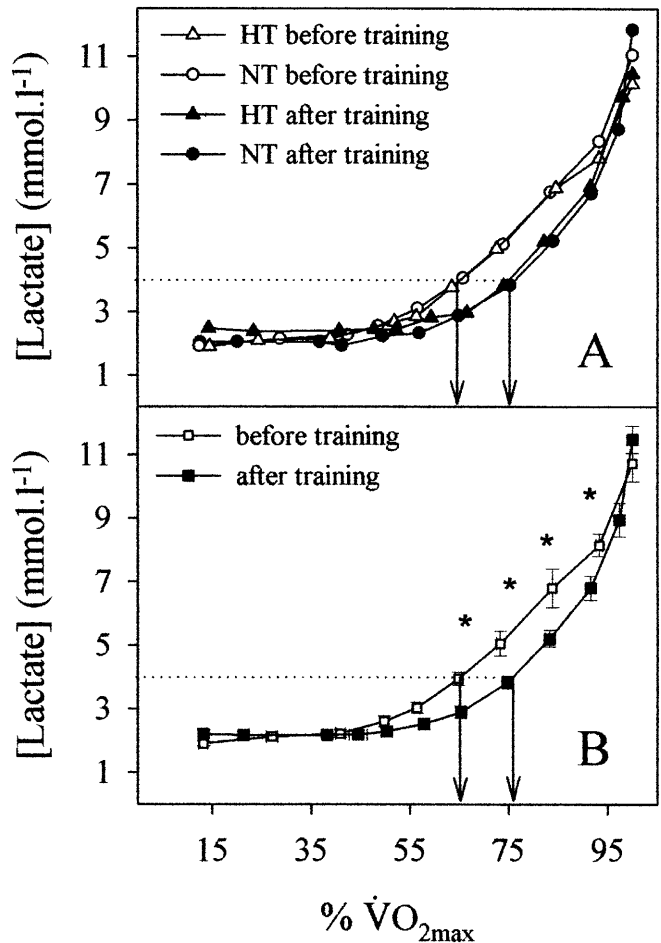


Fig. 1 Time courses of arterialized blood lactate concentrations obtained before (*open symbols*) and after (*closed symbols*) 4 weeks of endurance training for (A) the group of subjects ($n=5$) who trained in conditions of normobaric hypoxia (HT, triangles) and the group of subjects ($n=8$) who trained in conditions of normoxia (NT, circles), and (B) for the whole population of subjects ($n=13$, squares), during incremental exercises up to exhaustion in normoxia. Data are presented as the means (A) or means \pm SE (B). The arrows indicate the percentage of maximal oxygen uptake corresponding to the 4 $\text{mmol}\cdot\text{l}^{-1}$ blood lactate concentration (AT4%) before and after training. *Significant differences ($P < 0.05$) between pre- and post-training values

absolute work rates developed after training by the two groups of subjects during the CLE were similar (Table 4). Furthermore, the two groups of subjects were closely matched on the basis of their post-training blood lactate responses during the IE (Fig. 1A) as well as during the recovery from the CLE tests (Fig. 2A). Consequently,

trained in conditions of normobaric hypoxia, NT group of subjects who trained in conditions of normoxia). There were no significant differences between the averages of the two groups

Experimental group	Age (years)	Height (cm)	Body mass (kg)	$\dot{V}O_{2\max}$ ($\text{l}\cdot\text{min}^{-1}$)	$\dot{W}_{\text{aer,max}}$ ($\text{W}\cdot\text{kg}^{-1}$)
HT (SH1–SH5; $n=5$)	20.2 (0.4)	176 (6)	73.8 (11.2)	2.85 (0.28)	3.03 (0.26)
NT (S1–S8; $n=8$)	20.8 (0.7)	175 (4)	67.9 (4.0)	2.95 (0.22)	3.19 (0.13)

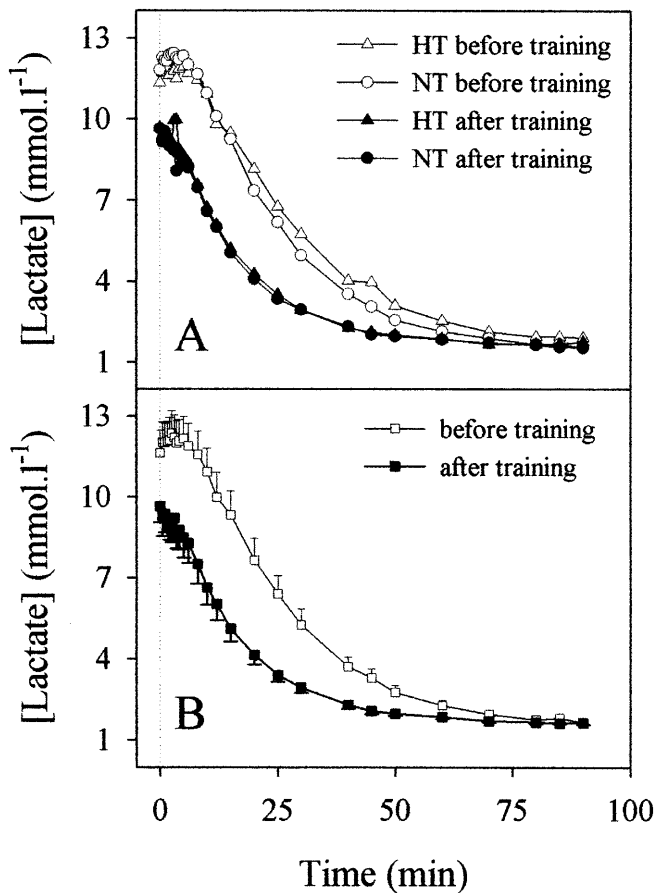


Fig. 2 Time courses of arterialized blood lactate concentrations during recovery from exercise performed at 90% maximal aerobic power in normoxic conditions before (*open symbols*) and after (*closed symbols*) 4 weeks of endurance training for (A) the HT ($n=5$, *triangles*) and the NT ($n=8$, *circles*) groups, and (B) for the whole population of subjects ($n=13$, *squares*). Data are presented as the means (A) or means \pm SE (B). Blood lactate concentrations are significantly lower ($P < 0.05$) post- than pre-training from the end of exercise up to the 50th min of recovery

there were no significant differences in the parameters of the fits to the recovery curves between HT and NT after training (Table 2). As shown in Table 2, there were also no statistically significant intergroup differences for the post-training average vastus lateralis muscle metabolic and histochemical characteristics. If the HT and NT groups were closely matched on the basis of their pre- and post-training parameter values, the factorial analysis revealed nevertheless a significant training effect on most of the studied parameters.

Specific effects of endurance training

The specific effects of 4 weeks of endurance training were determined by a comparison of the pooled pre- and post-training data. The average values of the blood lactate concentrations during the IE and after the CLE are shown in Figs. 1B and 2B, respectively. During the IE, the AT4% values were higher (by 14.7%; $P < 0.001$)

Table 2 Individual and mean (SE) values of the velocity constants γ_1 , γ_2 (denoting lactate exchange and removal abilities, respectively), and $La(0)$ (blood lactate concentration at time zero of the recovery) of the fits of Eq. 1 to the lactate recovery curves measured following 5 min exercise bouts performed by the HT and NT groups ($n=5$ and $n=8$, respectively) at 90% $\dot{W}_{aer,max}$ before and after training. There were no significant differences between the two experimental groups

Subject	γ_1 ($\cdot\text{min}^{-1}$)		γ_2 ($\cdot\text{min}^{-1}$)		$La(0)$ ($\text{mmol}\cdot\text{l}^{-1}$)	
	Before	After	Before	After	Before	After
HT group						
SH1	0.167	0.280	0.0438	0.0653	12.42	11.86
SH2	0.272		0.0732	0.0944	7.58	6.93
SH3	0.162	0.469	0.0586	0.0584	10.41	8.45
SH4	0.138	0.284	0.0392	0.0893	15.00	10.60
SH5	0.117	0.457	0.0564	0.0791	12.75	6.90
Mean	0.171	0.372 ^a	0.0542	0.0773	11.63	8.95
SE	0.027	0.053	0.0060	0.0069	1.25	1.00
NT group						
S1	0.387	0.417	0.0512	0.0988	7.63	6.18
S2	0.123	0.231	0.0388	0.0672	13.40	11.06
S3	0.189	0.264	0.0626	0.0505	9.20	9.82
S4	0.302	0.786	0.0434	0.0692	9.44	4.65
S5	0.142	0.141	0.0717	0.1068	12.28	9.08
S6	0.176	0.281	0.0580	0.0893	13.90	10.02
S7	0.273	0.198	0.0608	0.0734	13.02	13.10
S8	0.150	0.222	0.0511	0.1021	13.73	8.24
Mean	0.218	0.318	0.0547	0.0822	11.58	9.02
SE	0.033	0.073	0.0038	0.0071	0.87	0.95

^a Mean of only four values

after training (Fig. 1B). The average post-training blood lactate concentrations were lower ($P < 0.05$) than the corresponding pre-training values, from $\cong 65$ –90% $\dot{V}O_{2max}$ (Fig. 2B). Time courses of lactate concentrations after CLE were lower ($P < 0.05$) after training. They remained so until the 50th min of the passive recovery (Fig. 2B).

Table 5 gives the mean parameters of the fits to the lactate recovery curves before and after training for the whole population of subjects. The velocity constants γ_1 and γ_2 were consistently improved by training (by 68 and 47%, respectively), while the absolute values of the measured $La(0)$ and fitted concentration parameters A_1 and A_2 were significantly decreased (by 22%, 39% and 35%, respectively).

The histological and enzyme characteristics of the vastus lateralis muscle are reported in Table 3. Training resulted in an increase in the surface area of slow-twitch (ST) and fast-twitch type a (FTa) fibers by 10.8% ($P < 0.01$) and by 11.0% ($P < 0.05$), respectively. The number of capillaries in contact with ST, FTa and fast-twitch type b (FTb) fibers, as well as the capillary density were significantly larger after training. On the other hand, the fiber-type distribution was unchanged in pre-compared to post-training trials. While CS activity increased after training, PFK activity was unchanged and LDH activity decreased. The proportion of the H isozyme of lactate dehydrogenase (H-LDH) increased with training (by 24%; $P < 0.05$), in contrast to that of the M

Table 3 Some histological and enzyme characteristics of the vastus lateralis muscle before and after 4 weeks of endurance training for the HT and NT groups ($n=5$ and $n=8$, respectively), and for the whole population of subjects ($HT+NT$, $n=13$). Data are presented

as the mean (SE). (*ST* Slow-twitch fiber, *FT* fast-twitch fiber, *PFK* phosphofructokinase, *CS* citrate synthase, *LDH* lactate dehydrogenase, *H-LDH* the H isoform proportion of LDH, *M-LDH* the M isoform proportion of LDH)

Parameter	Pre-training			Post-training			
	HT	NT	HT+NT	HT	NT	HT+NT	HT+NT
Fiber type distribution (%)							
ST	39.2 (6.2)	40.4 (2.9)	39.9 (2.8)	40.9 (6.2)	38.1 (3.9)	39.2 (3.2)	
FTa	31.4 (5.8)	31.9 (3.4)	31.8 (2.9)	28.5 (2.3)	34.6 (2.7)	32.2 (2.0)	
FTb	27.7 (4.7)	25.1 (3.5)	26.1 (2.7)	25.1 (4.1)	23.5 (1.9)	24.1 (1.9)	
FTc	1.7 (0.8)	2.6 (1.3)	2.2 (0.8)	5.4 (3.3)	3.8 (2.0)	4.5 (1.7)	
Fiber cross-sectional area (μm^2)							
ST	3977 (201)	5025 (373)	4622 (277)	4530 (225)	5494 (329)	5123 (252)**	
FTa	5359 (482)	5375 (363)	5369 (277)	6110 (667)	5863 (479)	5958 (375)*	
FTb	4208 (506)	4159 (237)	4178 (230)	5160 (707)	4018 (253)	4457 (336)	
FTc	603 (603)	1061 (709)	885 (481)	2237 (1525)	745 (745)	1319 (736)	
Capillaries in contact per fiber, and capillary density							
ST	4.16 (0.17)	4.45 (0.19)	4.34 (0.14)	5.64 (0.15)	6.11 (0.36)	5.93 (0.23)**	
FTa	4.54 (0.28)	4.36 (0.17)	4.43 (0.14)	5.78 (0.32)	5.78 (0.28)	5.78 (0.22)**	
FTb	3.34 (0.16)	3.38 (0.21)	3.36 (0.14)	4.34 (0.32)	4.18 (0.28)	4.24 (0.20)**	
Density ($\cdot\text{mm}^2$)	328 (27)	367 (16)	351 (15)	431 (37)	475 (27)	459 (22)**	
Enzyme activities ($\mu\text{mol}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$ dry muscle)							
PFK	158 (13)	139 (7)	147 (7)	152 (22)	134 (17)	141 (13)	
CS	18.2 (1.24)	18.2 (1.28)	18.19 (0.88)	25.1 (0.96)	28.1 (3.13)	26.92 (1.95)**	
LDH	896 (196)	1009 (134)	965 (108)	780 (193)	765 (101)	771 (92)**	
Proportion of LDH isozymes (%)							
H-LDH	18.2 (3.6)	20.6 (2.8)	19.7 (2.1)	22.1 (4.8)	25.8 (3.0)	24.4 (2.5)*	
M-LDH	81.8 (3.6)	79.4 (2.8)	80.3 (2.1)	77.9 (4.8)	74.2 (3.0)	75.6 (2.5)*	

Statistical significance between the corresponding values obtained before and after 4 weeks of endurance training (Wilcoxon signed ranked test): * $P < 0.05$; ** $P < 0.01$

Table 4 Heart and work rates during the 5-min exercise bout at 90% $\dot{W}_{\text{aer,max}}$ before training (*Pre-training*), during the 4-week training period, and after training (*Post-training*) in the NT and HT

groups. Data are presented as the mean (SE) of $n=5$ for the HT group and $n=8$ for the NT group. (*NM* Not measured, *NS* not significant)

Group	Pre-training	Week 1	Week 2	Week 3	Week 4	Post-training
Heart rate ($\text{beats}\cdot\text{min}^{-1}$)						
HT	NM	160 (5)	162 (5)	167 (4)	168 (4)	NM
NT	NM	165 (5)	166 (4)	167 (4)	168 (4)	NM
Statistical significance		NS	NS	NS	NS	
Work rates ($\text{W}\cdot\text{kg}^{-1}$)						
HT	2.73 (0.23)	1.60 (0.13)	2.05 (0.14)	2.21 (0.12)	2.30 (0.15)	3.15 (0.27)***
NT	2.87 (0.11)	2.07 (0.07)	2.35 (0.08)	2.54 (0.09)	2.71 (0.12)	3.31 (0.14)***
Statistical significance	NS	**	**	**	*	NS

Difference between the HT and NT groups, * $P < 0.06$, ** $P < 0.05$; (Mann-Whitney U test). Difference between pre- and post-training for the HT and NT groups, *** $P < 0.05$; (Wilcoxon signed-rank test)

isoform of lactate dehydrogenase, which decreased ($P < 0.05$).

Discussion

Effect of oxygen partial pressure during training

The adaptations brought about by training on the sea-level $\dot{W}_{\text{aer,max}}$ (Table 4), blood lactate time courses during IE or after CLE (Figs. 1, 2), parameters of the fits γ_1 and γ_2 (Table 2), and the muscular metabolic and histochemical characteristics investigated (Table 3)

were of the same magnitude and direction among the HT and the NT subjects. Previous studies have found that training at the same relative work rates in normobaric hypoxia and in normoxia results in similar effects on sea-level $\dot{V}\text{O}_{2\text{max}}$ (Engfred et al. 1994), endurance time (Emonson et al. 1997), lactate threshold (Terrados et al. 1988) and mitochondrial volume densities (Desplanches et al. 1993). Taken together, these data put into question the potentiating effects of hypoxia during training, especially when training in normoxia and in hypoxia has been performed at the same relative work rates (Böning 1997; Melissa et al. 1997).

If the two training regimens have the same consequences, it can reasonably be assumed that training performed at the same relative work rate in normobaric hypoxia or in normoxia corresponds to the same stimulus for muscle adaptation. Different stimuli regulate the gene expression in the fibers affected by the exercise. Hypoxia is a very strong candidate as a stimulus for muscle adaptation (Booth and Baldwin 1996). Terrados et al. (1990) found a larger increase in the oxidative (CS) enzyme activities in the muscles of the leg trained in a hypobaric chamber than in the leg trained at the same absolute work load in normoxia. If one cannot totally exclude the hypothesis that in the present study hypoxia was not sufficient (in terms of duration) to create additional adaptations in the HT group, it is nevertheless important to note that hemoglobin saturation was significantly lower in hypoxia than in normoxia [e.g., 80.1 (0.8)% vs 95.8 (0.3)% at exhaustion during IE, $P < 0.001$]. Therefore, the similar training-induced adaptations of HT and NT might be related to the fact that both groups trained at the same relative work rates (i.e., at a higher absolute work load for NT; Table 4). The higher rate of ATP turnover in NT may serve as an additional signal to up-regulate their muscle adaptations (Booth and Baldwin 1996). In other words, it is possible that in the present study, the hypoxic up-regulation expected for the HT group was similar to the up-regulation linked to the higher absolute work load (metabolic flux) performed during training by the NT group. An alternative explanation would be that in the present study, hypoxic and normoxic training at the same relative work rate resulted in the same cellular hypoxia, and consequently led to the same cellular adaptations. The similar effects in HT and NT might also be related to the fact that stimulation of the β -adrenergic receptors involved in oxidative adaptations to endurance training (Booth and Baldwin 1996) was identical for HT and NT during training. A previous study (Kjær et al. 1988) reported that epinephrine as well as norepinephrine responses to exercise were similar whether the exercise was performed at the same relative work rates in hypoxia or in normoxia. Finally, if one considers heart rate to be an indicator of the metabolic load for the muscle tissues in exercise, it is then interesting to note that the HT and NT groups displayed the same heart rates during the training sessions (Table 4).

Effect of training on the lactate exchange ability

In the present study, 4 weeks of endurance training resulted in a 68% increase in γ_1 (Table 5). In view of the functional signification attributed to this rate constant (Freund et al. 1986; Freund and Zouloumian 1981), this finding means that endurance training improves the lactate exchange ability between the previously worked muscles and the blood. This is the first time a longitudinal study has reported an in vivo training-induced improvement of the lactate exchange ability in humans.

Several training-induced adaptations might explain such an improvement. Endurance training is known to shift the fiber-type distribution toward a higher percentage of oxidative fibers (Åstrand and Rodahl 1986), in which the lactate transport capacity is higher than in the glycolytic fibers (Juel 1997). However, this explanation cannot be retained for the present study, since training did not modify the fiber-type distribution for our subjects (Table 3). On the other hand, the significant increase in the capillary supply and density obtained in the present study would increase the exchange area and decrease the diffusion distance between the site of production and the capillary wall. This might explain, at least in part, the observed improvement in the lactate exchange ability. Earlier, Pilegaard et al. (1994) mentioned that sarcolemmal carrier-mediated lactate transport, which has an important role in lactate release during and after heavy exercise (Dubouchaud et al. 2000), is higher in athletes than in less-fit or untrained subjects. A longitudinal study on the sarcolemmal giant vesicles of the rat showed that 7 weeks of training ($\cong 90\% \dot{V}O_{2\max}$) induced an increase in the capacity to transport lactate via carrier-mediated processes by reducing the transporter affinity (K_m) and by increasing the maximal transport capacity (V_{\max}) (Pilegaard et al. 1993). Juel (1997) does not exclude that synthesis of new transporter proteins accounting for training adaptations may contribute to these lactate transport capacity improvements. This is consistent with the recent findings of Bonen et al. (1998) and Pilegaard et al. (1999), who observed that the training-induced improvement of muscle lactate transport capacity is associated with an increase in MCT1 and MCT4, two isoforms of a membrane-bound monocarboxylate transporter that is a

Table 5 Parameters of the fits of Eq. 1 to the lactate recovery curves from the 5 min exercise performed at 90% $\dot{W}_{\text{aer,max}}$ before and after training for the whole population of subjects ($n = 13$).

Values are presented as the means (SE). A_1 and A_2 are the amplitudes of the two exponential terms of Eq. 1

Time point	A_1 (mmol·l ⁻¹)	γ_1 (min ⁻¹)	A_2 (mmol·l ⁻¹)	γ_2 (min ⁻¹)	La(0) (mmol·l ⁻¹)	$\gamma_1:\gamma_2$ ratio
Before training	8.99 (1.43)	0.200 (0.023)	-19.23 (1.97)	0.0545 (0.0031)	11.60 (0.69)	3.77 (0.47)
After training	5.45 (1.22)	0.336 (0.051)	-12.37 (1.66)	0.0803 (0.0049)	8.99 (0.67)	4.57 (0.81)
Statistical significance	*	*	*	*	*	NS

Statistical significance between the values obtained before and after 4 weeks of endurance training (Wilcoxon signed ranked test), * $P < 0.01$. NS not significant

critical protein for the transport of lactate across the sarcolemma.

Time courses of the net lactate release rate (LER, $\text{mmol}\cdot\text{min}^{-1}$) from the muscle to the blood calculated during recovery from the product of arterio-venous differences and muscle blood flow, can be fitted to a decreasing exponential time function (where a is the amplitude of the exponential term):

$$\text{LER} = a \cdot e^{-\beta t} \quad (2)$$

The velocity constant β of the fits of Eq. 2 to the data of Bangsbo et al. (1993) and Juel et al. (1990) after exhaustive exercise bouts (0.274 and $0.331\cdot\text{min}^{-1}$, respectively) are very close to the γ_1 values reported in Table 5. Furthermore, Juel (1997) has recently compared rate constants for lactate efflux from human sarcolemmal vesicles to γ_1 values. The constant he obtained ($0.46\cdot\text{min}^{-1}$) is of the same magnitude as the γ_1 values we found after training (Table 5).

Effects of training on the lactate removal ability

Lampert et al. (1996) reported that improvements in the physical condition of the subjects in response to endurance training are associated with a concomitant increase in the ability to remove lactate during the recovery when exercise is performed at the same absolute work rate before and after training. A comparable training-induced increase in γ_2 has also been found in the present study, but the originality of our finding is that its rise is significant even when the exercise preceding the recovery is performed at the same relative high work rate before and after training. This finding does not agree with the results of Bassett et al. (1991) or Oosthuysen and Carter (1999), who concluded that training status has no effect on the lactate removal ability during recovery after 3-min cycling exercise bouts leading to the same end exercise blood lactate concentrations ($\text{La}(0)$) (Bassett et al. 1991) or after IEs (Oosthuysen and Carter 1999). Differences in the experimental conditions might explain the discrepancy. First, the spread of the interindividual differences of the subjects may have masked the improvement in γ_2 that is attributable to training in these earlier cross-sectional studies (Bassett et al. 1991; Oosthuysen and Carter 1999). Second, it is also likely that the training-induced improvement in γ_2 was counterbalanced by the inhibitory effect on γ_2 of the higher absolute and relative work rates (Freund et al. 1986; Oyono-Engu  ll   and Freund 1992) performed by the group of trained subjects during IE (Oosthuysen and Carter 1999) or 3-min exercise bouts (Bassett et al. 1991).

Nonetheless, the training-induced improvement in γ_2 observed in the present study is in accordance with the results obtained during exercise at lower relative work rates by MacRae et al. (1992), and more recently by Bergman et al. (1999) with tracers. Specifically, these authors observed that the MCR of lactate (the product of the fractional turnover rate and the lactate space)

was increased during exercise performed at $65\% \dot{V}\text{O}_{2\text{max}}$ (Bergman et al. 1999) or at all relative work rates lower than $75\% \dot{V}\text{O}_{2\text{max}}$ (MacRae et al. 1992) after 9 weeks of endurance training. Despite the fact that our data were taken during recovery, it seems of interest to compare the numerical values of the MCR during recovery (MCRR) obtained by the present methodology with the MCR measured during exercise. MCRR can be approximated by means of the following equation:

$$\text{MCRR} = V_{\text{TLS}} \cdot \gamma \quad (3)$$

where V_{TLS} is the total lactate space (i.e., $500\text{ ml}\cdot\text{kg}^{-1}$ body mass). In the study of Bergman et al. (1999), training increased the MCR measured during exercise performed at $65\% \dot{V}\text{O}_{2\text{max}}$ from $28\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to $48\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. During a progressive exercise, MacRae et al. (1992) measured an MCR of $31\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at $\cong 75\%$ of $\dot{V}\text{O}_{2\text{max}}$; 9 weeks of endurance training later, the MCR measured at the same relative work rate rose to $40\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (MacRae et al. 1992). It is then interesting to note that the MCRR computed by means of γ_2 obtained in the present study increased from $27.5\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to $40\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. This comparison underlines the strong analogy between the results obtained by the present methodology during recovery and those obtained by other authors with tracers during exercise.

Beyond $75\% \dot{V}\text{O}_{2\text{max}}$, no data from tracer studies are available in the literature because this technique has a methodological limitation: for reliable measurements, blood lactate concentrations must be at a steady-state level. This excludes the investigation of the lactate metabolism for relative high-intensity exercises. On the other hand, the biexponential time function (Eq. 1) fits accurately a large variety of blood lactate recovery curves, including those obtained following high relative exercise work rates (Freund and Zouloumian 1981). This is a major argument in favor of the use of the biexponential model.

A better lactate removal ability may indicate an increased utilization of lactate as an energetic substratum. Among the possible fates of lactate during recovery, the major one is oxidation by skeletal muscles (Brooks 1986; Donovan and Pagliassotti 2000). An increase in lactate-to-pyruvate oxidation and in pyruvate oxidation via the Krebs cycle can be assumed to be the metabolic basis of the lactate removal ability improvement. The significant increases of the H-LDH proportion and CS activity obtained in the present study lend support to this hypothesis (Table 3).

Training-induced improvement in γ_1 and γ_2 : physiological consequences

The training-induced improvements in γ_1 and γ_2 are important, especially during intense exercise. Insofar as lactate and protons are partly co-transported (Juel

1997), an improved lactate exchange ability by promoting an elevated proton exchange ability would prevent indirectly an early fall in intramuscular pH, which in turn would delay local fatigue (Fitts 1994). Furthermore, a better overall ability to remove lactate would result in a lower accumulation of lactate during exercise, not only in the blood but also in the active skeletal muscles. From a functional point of view, the lowered lactate concentrations in the active muscles and blood would contribute to a better maintenance of cellular homeostasis, which might result in a performance improvement (Pilegaard et al. 1994). In line with this assumption, a recent study has demonstrated that the individual performance of highly-trained oarsmen on a rowing ergometer is positively related to their lactate exchange and removal abilities (Messonnier et al. 1997).

In conclusion, 4 weeks of endurance training in normobaric hypoxia modified the blood lactate recovery curves and the lactate exchange and removal abilities in the same direction and in the same proportions as normoxic training. This result can be explained mainly by the fact that the training was performed at the same relative work rate for both conditions of oxygen partial pressure. Furthermore, endurance training per se increased significantly the lactate exchange and removal abilities determined in vivo during recovery from CLE performed at the same relative work rate before and after training. Finally, the present methodology permits in vivo non-invasive assessment of two important parameters of lactate kinetics, namely, the lactate exchange and removal abilities, in the unsteady state in humans. The fact that the results obtained during recovery by the present methodology are comparable to those obtained during exercise by other methods is probably not coincidental.

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References

- Andersen (1975) Capillary density in skeletal muscle of man. *Acta Physiol Scand* 95:203–205
- Åstrand PO, Rodahl K (1986) Textbook of work physiology. McGraw-Hill, New York
- Bangsbo J, Johansen L, Graham T, Saltin B (1993) Lactate and H^+ effluxes from human skeletal muscles during intense, dynamic exercise. *J Physiol (Lond)* 462:115–133
- Bassett DRJ, Merrill PW, Nagle FJ, Agre JC, Sampedro R (1991) Rate decline in blood lactate after cycling exercise in endurance-trained and untrained subjects. *J Appl Physiol* 70:1816–1820
- Bergman BC, Wolfel EE, Butterfield GE, Lopaschuk GD, Casazza GA, Horning MA, Brooks GA (1999) Active muscle and whole body lactate kinetics after endurance training in men. *J Appl Physiol* 87:1684–1696
- Bonen A, McCullagh JA, Putman CT, Hultman E, Jones NL, Heigenhauser GJF (1998) Short-term training increases human muscle MCT1 and femoral venous lactate in relation to muscle lactate. *Am J Physiol* 274:E102–E107
- Böning D (1997) Altitude and hypoxia training – a short review. *Int J Sports Med* 18:565–570
- Booth FW, Baldwin KM (1996) Muscle plasticity: energy demand and supply processes. In: Rowell LB, Shepherd JT (eds) *Handbook of physiology*, vol 12. Oxford University Press, New York, pp 1075–1123
- Brooke MH, Kaiser KK (1970) Muscle fiber types: how many and what kind? *Arch Neurol* 23:369–379
- Brooks GA (1986) The lactate shuttle during exercise and recovery. *Med Sci Sports Exerc* 18:360–368
- Brooks GA, Wolfel EE, Groves BM, Bender PR, Butterfield GE, Cymerman A, Mazzeo RS, Sutton JR, Wolfe RR, Reeves JT (1992) Muscle accounts for glucose disposal but not blood lactate appearance during exercise after acclimatization to 4,300 m. *J Appl Physiol* 72:2435–2445
- Brooks GA, Wolfel EE, Butterfield GE, Cymerman A, Roberts C, Mazzeo RS, Reeves JT (1998) Poor relationship between arterial [lactate] and leg net release during exercise at 4,300 m altitude. *Am J Physiol* 275:R1192–R1201
- Desplanches D, Hoppeler H, Linossier MT, Denis C, Claassen H, Dormois D, Lacour J-R, Geysant A (1993). Effects of training in normoxia and normobaric hypoxia on human muscle ultrastructure. *Pflügers Arch* 425:263–267
- Donovan CM, Pagliassotti MJ (2000). Quantitative assessment of pathways for lactate disposal in skeletal muscle fiber types. *Med Sci Sports Exerc* 32:772–777
- Dubouchaud H, Butterfield GE, Wolfel EE, Bergman BC, Brooks GA (2000) Endurance training, expression, and physiology of LDH, MCT1, and MCT4 in human skeletal muscle. *Am J Physiol* 278:E571–E579
- Emonson DL, Aminuddin AH, Wright RL, Scroop GC, Gore CJ (1997) Training-induced increases in sea level $\dot{V}O_{2max}$ and endurance are not enhanced by acute hypobaric exposure. *Eur J Appl Physiol* 76:8–12
- Engfred K, Kjaer M, Secher NH, Friedman DB, Hanel B, Nielsen OJ, Bach FW, Galbo H, Levine BD (1994) Hypoxia and training-induced adaptation of hormonal responses to exercise in humans. *Eur J Appl Physiol* 68:303–309
- Essen-Gustavsson B, Henriksson J (1984) Enzymes levels in pools of microdissected human muscle fibres of identified type. *Acta Physiol Scand* 120:505–515
- Fitts RH (1994) Cellular mechanisms of muscle fatigue. *Physiol Rev* 74:49–94
- Freund H, Zouloumian P (1981) Lactate after exercise in man. *Eur J Appl Physiol* 46:121–176
- Freund H, Oyono-Enguèllé S, Heitz A, Marbach J, Ott C, Zouloumian P, Lampert E (1986) Work rate-dependent lactate kinetics after exercise in humans. *J Appl Physiol* 61:932–939
- Geysant A, Dormois D, Barthelemy J-C, Lacour J-R (1985) Lactate determination with the analyser L.A. 640: a critical study. *Scand J Clin Lab Invest* 45:145–149
- Ingjer F (1979) Effects of endurance training on muscle fiber ATPase activity, capillary supply and mitochondrial content in man. *J Physiol (Lond)* 294:419–432
- Juel C (1997) Lactate-proton cotransport in skeletal muscle. *Physiol Rev* 77:321–358
- Juel C, Bangsbo J, Graham T, Saltin B (1990) Lactate and potassium fluxes from human skeletal muscle during and after intense, dynamic knee extensor exercise. *Acta Physiol Scand* 140:147–159
- Kjaer M, Bangsbo J, Lortie G, Galbo H (1988) Hormonal response to exercise in humans: influence of hypoxia and physical training. *Am J Physiol* 254:R197–R203
- Lampert E, Oyono-Enguèllé S, Mettauer B, Freund H, Lonsdorfer J (1996) Short endurance training improves lactate removal ability in patients with heart transplants. *Med Sci Sports Exerc* 28:801–807
- Lowry OH, Passonneau JV (1972) A flexible system of enzymatic analysis. Academic, New York, pp 93–108
- MacRae HSH, Dennis SC, Bosch AN, Noakes TD (1992) Effects of training on lactate production and removal during progressive exercise in humans. *J Appl Physiol* 72:1649–1656

- Mansour TE (1966) Studies on heart phosphofructokinase: purification, inhibition and activation. *J Biol Chem* 238:2285–2292
- Melissa L, MacDougall JD, Tarnopolsky MA, Cipriano N, Green H (1997) Skeletal muscle adaptations to training under normobaric hypoxic versus normoxic conditions. *Med Sci Sports Exerc* 29:238–243
- Messonnier L, Freund H, Bourdin M, Belli A, Lacour J-R (1997) Lactate exchange and removal abilities in rowing performance. *Med Sci Sports Exerc* 29:396–401
- Oosthuysen T, Carter RN (1999). Plasma lactate decline during passive recovery from high-intensity exercise. *Med Sci Sports Exerc* 31:670–674
- Oyono-Enguélé S, Freund H (1992) Ability to remove lactate in endurance-trained and endurance-untrained humans. *J Appl Physiol* 72:396–398
- Pilegaard H, Juel C, Wibrand F (1993) Lactate transport studied in sarcolemmal giant vesicles: effects of training. *Am J Physiol* 264:E156–E160
- Pilegaard H, Bangsbo J, Richter EA, Juel C (1994) Lactate transport studied in sarcolemmal giant vesicles from human biopsies: relation to training status. *J Appl Physiol* 77:1858–1862
- Pilegaard H, Domino K, Noland T, Juel C, Hellsten Y, Hallestrap A P, Bangsbo J (1999) Effect of high-intensity exercise training on lactate/H⁺ transport capacity in human skeletal muscle. *Am J Physiol* 276:E255–E261
- Rosalki SB (1974) Standardisation of isoenzyme assays with special reference to lactate dehydrogenase isoenzyme electrophoresis. *Clin Biochem* 7:29–40
- Terrados N, Melichna J, Sylven C, Jansson E, Kaijser L (1988) Effects of training at simulated altitude on performance and muscle metabolic capacity in competitive road cyclists. *Eur J Appl Physiol* 57:203–209
- Terrados N, Jansson E, Sylven C, Kaijser L (1990) Is hypoxia a stimulus for synthesis of oxidative enzymes and myoglobin? *J Appl Physiol* 68:2369–2372
- Tesch PA, Wright JE (1983) Recovery from short-term intense exercise: its relation to capillary supply and blood lactate concentration. *Eur J Appl Physiol* 52:98–103