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Lactate Removal Ability and $\dot{V}O_2$ Recovery Kinetics in Sickle Cell Trait Carriers Compared with Normal Haemoglobin Subjects: Preliminary Data

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Abstract: Because of the reduced affinity of haemoglobin S to oxygen and the altered blood rheological profile of sickle cell trait carriers (AS), it is often thought that exercise physiological responses should differ between AS and subjects with normal haemoglobin (AA). The present study aimed to compare the ability to remove blood lactate and the characteristics of oxygen uptake ($\dot{V}O_2$) recovery kinetics after supramaximal exercise in eight AS and eight matched AA. All subjects performed a supramaximal exercise test consisting of pedalling for 1 min at 110% maximal $\dot{V}O_2$. Following exercise, venous blood samples were obtained from AS and AA at different times to assess blood lactate concentrations. Mathematical modelling was applied during recovery to assess the blood lactate removal ability (time constant γ_2) and the kinetics for $\dot{V}O_2$ recovery (amplitude A_2 and time constant τ_2). Lactate removal ability and the $\dot{V}O_2$ recovery kinetics were not significantly different between the two groups ($P > 0.05$). No significant relationship was observed between γ_2 and A_2 ($r = 0.04$; $P > 0.05$) or between γ_2 and τ_2 ($r = -0.44$; $P > 0.05$) in all groups. It seems that the ability to recover or to remove lactate after a short supramaximal exercise does appear unaltered by sickle cell trait. It is possible that the elevated blood viscosity reported several times in AS could have promoted greater vasodilatation which in turn may favour exercise recovery to a similar level observed in subjects with normal haemoglobin. Our findings may suggest that AS and AA subjects need similar recovery after exhausting exercise. However, it is also known that AS may be prone to medical complications in response to exercise. So, the presence of clinical sign should justify to prolong recovery or to stop exercise in AS.

Keywords: Haemoglobin S, EPOC, Exercise, Anaerobic metabolism.

INTRODUCTION

Sickle cell trait (SCT) is the heterozygous form of sickle cell disease (SCD), which is the most prevalent genetic abnormality in the world. SCT is marked by the presence of both normal and abnormal haemoglobin (i.e. HbA and HbS, respectively) in red blood cells (RBCs).

The presence of both HbA and HbS led previous investigators to hypothesize that SCT carriers (AS) would have different physiological responses to exercise than subjects with normal Hb (AA) [1-5]. Because the presence of HbS into RBCs might change the oxygen-carrying properties of these cells [6] and because the increased blood viscosity found in AS could disturb blood flow and oxygen delivery to

tissues [7], one of the often discussed particularities of AS concerns lactate metabolism during exercise [5]. We tried to revisit the question of whether lactate metabolism regulation is different between AS and AA using bi-exponential modelling of lactate recovery curves [3, 8, 9] after a short strenuous exercise resulting in profound metabolic acidosis [10]. This mathematical model, instead of the isotope tracer method, has the advantage to be applied to non steady-state, supramaximal conditions.

Several studies have also focused on how lactate affects the recovery of oxygen consumption after exercise (i.e. on the excess postexercise oxygen consumption; EPOC). Using a radioactive tracer technique, Brooks *et al.* [11] demonstrated that a causal relationship between lactate and the slow component of EPOC is unlikely. On the other hand, several studies [12, 13] have shown results supporting the concept that lactate influences the slow component of EPOC time course. As lactate may be related to EPOC, we hypothesised that if lactate removal ability differs between

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AS and AA, EPOC (and particularly the slow component phase) will also differ between the two populations.

The dual purpose of the present study was to compare the ability to remove lactate and its temporal association to the EPOC slow component after supramaximal exercise in AS and AA subjects matched for ethnic origin and overall physical fitness level. To test these hypotheses, we used the same participants and exercise protocol as in a previous study [7].

METHODS

Subjects

Eight male SCT carriers (AS group; 24.1 ± 3.2 yrs, 181.3 ± 1.7 cm, 76.0 ± 3.4 kg) and eight male subjects with normal haemoglobin (AA group; 19.6 ± 0.5 yrs, 179.0 ± 1.7 cm, 68.9 ± 2.7 kg) participated in the present study. The haematological characteristics of the subjects are summarised in Table 1. All were students at the University of the French West Indies and Guyana and took part in the same training programme. They were moderately trained and practised athletic activities regularly (12 ± 2.1 h/week) but never at a high level. The subjects who did not have the required training status or who were unwilling to follow the study protocol were excluded.

Table 1. Haematological Parameters in the Two Groups

		Hb (g.dL ⁻¹)	Hct (%)	Ret (%)	HbS (%)
Group	AS (n = 8)	14.7 ± 0.2	45.8 ± 0.7	0.96 ± 0.07	38.0 ± 0.8
	AA (n = 8)	14.5 ± 0.3	46.2 ± 0.4	1.19 ± 0.15	-

Values are means \pm SEM. Hb (haemoglobin), Hct (haematocrit), HbS (haemoglobin S), Ret (reticulocytes), (n) number of subjects. No significant difference between the two groups.

Protocol

At the beginning of the university year, all new students of the Faculty of Sports underwent haemoglobin screening. Eight AS subjects were detected in this screening programme and included in the study. Eight AA subjects were then selected and matched for maximal oxygen uptake ($\dot{V}O_2$ max) and anthropometric and haematological data (Table 1). Subjects with anaemia and/or alpha-thalassaemia were excluded. The subjects were informed of the procedures and purposes of the study, which was approved by the local Ethics Committee, and gave written consent to participate. The protocol was in accordance with the guidelines set by Declaration of Helsinki.

On the first experimental day, all athletes performed a progressive and maximal exercise test to determine the maximal power output (MAP) and $\dot{V}O_2$ max (data not shown and already published in [7]). One week later, the same subjects performed a supramaximal exercise test consisting of pedalling for 1 min at 110% $\dot{V}O_2$ max, during which oxygen uptake ($\dot{V}O_2$) was measured breath-by-breath. This type of supramaximal test is well-known to induce increased blood lactate during the first moments of recovery before its clearance and consequently is appropriate for mathematical

modelling of blood lactate recovery curves (see below). Venous blood samples were obtained from AS and AA at different times to assess the haematological parameters and blood lactate concentrations. No additional drink was allowed 3 hours before and during exercise and the subsequent recovery.

SCT Diagnosis and Blood Analysis

Techniques used for SCT diagnosis were the same than those previously used [14, 15]. To test for the haemoglobin type, venous blood was drawn into tubes containing EDTA (i.e. ethylenediaminetetraacetate) and screened by isoelectric focusing. The results were confirmed by citrate agar electrophoresis. The various haemoglobins were isolated and quantified by high performance liquid chromatography (HPLC). A test of solubility confirmed the presence of HbS. Positive test results for SCT were confirmed by the presence of HbS (< 50%) and a normal percentage of HbA₂ [16]. Haemoglobin concentration ([Hb]), haematocrit (Hct) and percentage of reticulocytes (% Ret) were also studied for the indirect diagnosis of anaemia and alpha-thalassaemia, which results in haematological modifications [17].

Incremental Exercise Test

The progressive and maximal exercise test began with a 3-min warm-up at 60 W. Pedalling frequency remained constant (at 70 rpm) throughout testing, and the load was increased by 30 W every minute until $\dot{V}O_2$ max was reached. Oxygen uptake was considered maximal if at least three of the following criteria were met: 1) a respiratory exchange ratio greater than 1.10; 2) attainment of age-predicted maximal heart rate (HR max) [$210 - (0.65 \times \text{age}) \pm 10\%$]; 3) an increase in $\dot{V}O_2$ lower than 100 ml with the last increase in work rate; and 4) an inability to maintain the required pedalling frequency (70 rpm) despite maximum effort and verbal encouragement. A 5-min recovery period was then implemented with 2 min of pedalling and 3 min at rest. $\dot{V}O_2$ was continuously measured using a breath-by-breath automated metabolic system (Vmax 229 D series, Sensormedics Corp., Yorba Linda, CA, USA). A 10-leads electrocardiogram (Hellige, Marquette Medical Systems, Germany) was monitored continuously.

Supramaximal Exercise Test

During this session, a catheter was inserted into the antecubital vein for blood sampling. Each subject warmed up at moderate intensity (50% of $\dot{V}O_2$ max) for 5 min on a cycle ergometer and then rested for 5 min. The supramaximal exercise test consisted of pedalling at 110% of $\dot{V}O_2$ max for 1 min on the cycle ergometer [10]. Then, all subjects recovered passively for 1 hour on the cycle ergometer and in the same sitting position as during the exercise. During recovery, $\dot{V}O_2$ was measured breath-by-breath during the first 10 min.

Blood Lactate Sampling and Analysis

Blood was sampled at rest, immediately at the end of exercise and at minutes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15,

20, 30, 40, 50 and 60 of the subsequent recovery. Blood for lactate measurements was sampled in EDTA tubes. An aliquot of 50 μl was rapidly analysed for blood lactate concentration using a testing strip (BM-Lactate, Roche Diagnostics, Mannheim, Germany) and an instrument for the resolution of lactate (Accusport, Boehringer Mannheim, Mannheim, Germany). This instrument has been demonstrated to be valid and reliable [18].

Mathematical Analyses

The individual lactate recovery curves were fitted using the following bi-exponential equation validated previously in the literature [8, 9, 19].

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

where $\text{La}(0)$ and $\text{La}(t)$ ($\text{mmol}\cdot\text{L}^{-1}$) are the lactate concentrations at the end of exercise and at any time t (min) of the recovery period, respectively; A_1 and A_2 ($\text{mmol}\cdot\text{L}^{-1}$) are the amplitudes of the two exponential components; and γ_1 and γ_2 (min^{-1}) are their respective velocity constants. The individual parameters of the bi-exponential function were fitted by means of an iterative nonlinear regression technique. Note that $\text{La}(0)$ was also adjusted to obtain the best fitting curves. The percentage of the variance explained by the use of the bi-exponential curve fit was determined by correlation of the observed and the predicted $\text{La}(t)$ at each time and by squaring of the Pearson-product correlation coefficient. The intervening mechanisms can be assimilated into two main processes: one with a velocity constant (γ_1) describing the blood lactate increase and the other with a velocity constant (γ_2) describing its decrease [3]. The velocity constants of the fitted exponential functions supply information on the ability to exchange lactate between the previously worked muscle and the remainder of the lactate space represented by the arterial blood (γ_1), and on the body's overall ability to remove lactate during recovery (γ_2) [8, 9]. Because lactate was analysed from venous blood samples, γ_2 has only a physiological meaning in this work, as in a previous work [19].

The $\dot{V}\text{O}_2$ recovery kinetics were modelled using the following equation validated previously in the literature [20, 21].

$$\begin{aligned} \dot{V}\text{O}_2(t) = & EE\dot{V}\text{O}_2 - A_1 [1 - e^{-(t-TD)/\tau_1}] \\ & \text{phase 1 (primary component)} \\ & - A_2 [1 - e^{-(t-TD)/\tau_2}] \\ & \text{phase 2 (slow component)} \end{aligned} \quad (2)$$

where $EE\dot{V}\text{O}_2$ is the end-exercise level of $\dot{V}\text{O}_2$, A_1 and A_2 are the amplitude terms, and τ_1 and τ_2 are the time constants of phases 1 and 2, respectively. The primary and slow components were constrained to begin at exercise offset, and we assumed that the two components were logically both "in operation" at the start of recovery. Thus, TD (value fixed to 0) is a common time delay for primary and slow components after the offset of exercise and t is the time in seconds from the downward transition.

As the initial "cardiodynamic" phase of the $\dot{V}\text{O}_2$ response does not directly represent active muscle O_2 utilisation, the first 20 s of the off-transient $\dot{V}\text{O}_2$ kinetics were omitted from

the fitting field [22]. Although the duration of this initial phase is likely to be less in recovery, as blood flow is higher at the off- than the on-transient, little is known about this duration and therefore omission of the first 20 s of the off-transient was thought to be more than sufficient to obviate any distorting influence on the subsequent kinetics.

Occasional errant data points caused by coughing, swallowing, sighing, etc., were deleted from the data set if they fell more than ± 4 SD outside the mean value for the 30-s interval that bracketed the breath in question [23]. The data were then smoothed using a rolling five-breath average procedure to reduce the noise and thus enhance the underlying characteristics [24].

The parameters of the mathematical model were determined from an iterative method (by using the Levenberg-Marquardt algorithm) by minimising the sum of the mean squares of the differences between the fitted $\dot{V}\text{O}_2$ and the experimental data (Solver from Excel 7.0, Microsoft Corporation). Iteration continued until successive repetitions reduced both the sum of residuals by $< 10^{-8}$ and the correlation coefficient of the relationship between residuals and time by $< 10^{-6}$ [25]. Plots of residuals were also examined to help determine the appropriate fits. Linear and non-linear regressions of the residuals against time were used to check a random distribution of the residual over a 0 value and to test the adequacy of the used model.

Statistical Analysis

The results are presented as means \pm SEM for all variables. A Student t test was used to compare anthropometric data, $\dot{V}\text{O}_2$ max, HR max, MAP, haematological parameters ([Hb], Hct and %Ret) and each parameter of the lactate recovery kinetics and the $\dot{V}\text{O}_2$ recovery kinetics. The time course of the blood lactate concentrations was compared between the two groups at rest, at the end of exercise and during recovery using a two-way (group \times time) analysis of variance (ANOVA) for repeated measures. Pair-wise contrasts were used when necessary to determine where significant differences had occurred. The relationship between lactate removal ability and the slow phase of the $\dot{V}\text{O}_2$ recovery kinetics was assessed using the Pearson correlation test. Statistical significance was established at $\alpha = 0.05$. Statistical analyses were conducted using Statistica (v. 5.5. Statsoft, USA).

RESULTS

Subject Characteristics, Haematological Parameters and Maximal Exercise Data

The AS and AA groups were similar for anthropometric data (age, height and weight) and haematological data (Table 1). As reported in previous publication [7], maximal exercise responses ($\dot{V}\text{O}_2$ max, HR max and MAP) did not differ between the groups.

Blood Lactate Recovery and EPOC Parameters

The mean blood lactate concentration never differed between the AS and AA (control) groups whatever the time

of measurement. We noted a time effect ($P < 0.05$) demonstrating higher adjusted blood lactate concentration from the end of exercise ($4.68 \pm 0.88 \text{ mmol.L}^{-1}$ and $3.83 \pm 0.59 \text{ mmol.L}^{-1}$ of [La] in AS and AA, respectively) until the 50th min of recovery as compared with rest ($1.51 \pm 0.13 \text{ mmol.L}^{-1}$ and $1.58 \pm 0.13 \text{ mmol.L}^{-1}$ of [La] in AS and AA, respectively). No significant difference was observed between rest and the 60th min of recovery ($1.61 \pm 0.15 \text{ mmol.L}^{-1}$ and $1.89 \pm 0.15 \text{ mmol.L}^{-1}$ of [La] in AS and AA, respectively). The mean blood lactate recovery curves of the two groups are presented in Fig. (1). The Fig. (2) is a representative blood lactate recovery curve in a SCT carrier. The mean values of the parameters obtained with Eq.1 after the 1-min 110% $\dot{V}O_2$ max exercise are reported in Table 2. The mean velocity constants γ_1 and γ_2 , as well as the concentration parameters A_1 , A_2 and $La(0)$, were not different between the two groups.

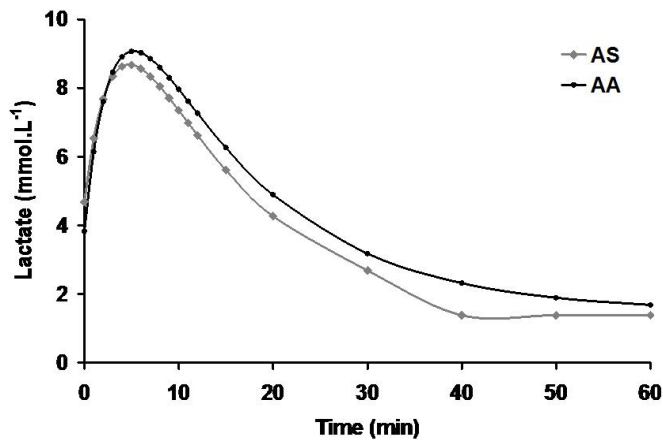


Fig. (1). Mean blood lactate recovery curves in the two groups. The two curves were not statistically different.

The parameters derived from the $\dot{V}O_2$ recovery kinetics are shown in Table 3. At this stage, because of a technical problem with the breath-by-breath automated metabolic system, modelling of four of the subjects (2 AS and 2 AA) was not completed. Therefore, the study of the $\dot{V}O_2$ recovery kinetics was conducted on six AS and six AA subjects. Neither the time constants nor amplitudes of the fast and slow components of $\dot{V}O_2$ recovery kinetics were significantly different between the two groups. The mean $\dot{V}O_2$ recovery kinetics curves of the two groups are presented in Fig. (3), and the Fig. (4) is showing a representative curve of a SCT carrier.

DISCUSSION

The dual purpose of the present study was to determine whether the ability to remove lactate (γ_2) and its temporal association to the slow component of $\dot{V}O_2$ recovery kinetics in response to a supramaximal exercise test were different between AS and AA. We found no significant difference in the ability to remove lactate between our two groups. Similarly, neither the EPOC slow component nor the fast component differed between the groups.

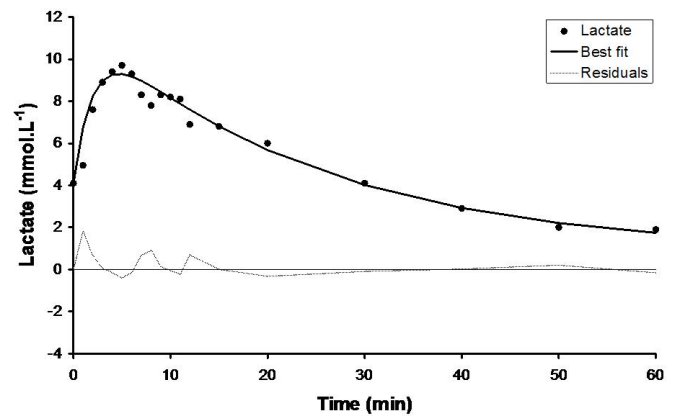


Fig. (2). Representative blood lactate recovery curve in a SCT carrier. Note the plot of residuals which demonstrates the good fitting procedure.

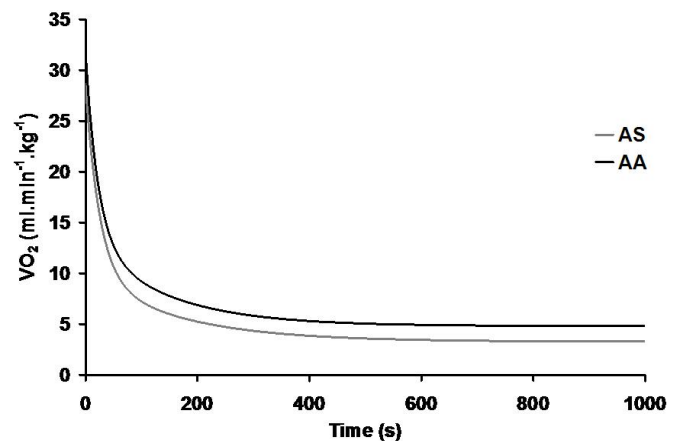


Fig. (3). Mean $\dot{V}O_2$ recovery kinetics curves in the two groups. The two curves were not statistically different.

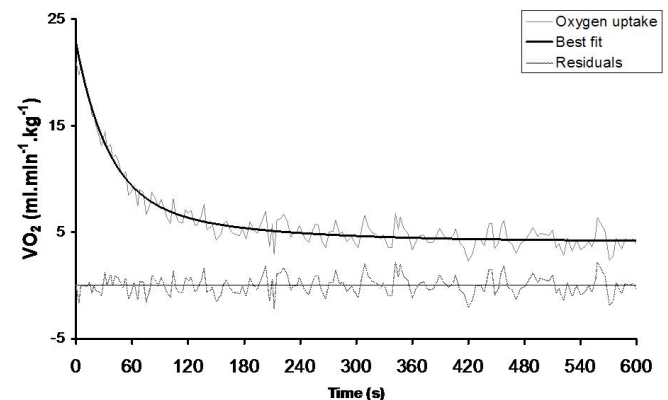


Fig. (4). Representative $\dot{V}O_2$ recovery kinetics curve in a SCT carrier. Note the plot of residuals which demonstrates the good fitting procedure.

Freund *et al.* [3] investigated the ability of AS to exchange and remove lactate from the blood circulation after a ramp exercise test and observed that AS were likely to produce more lactate than controls and/or to have an impaired ability to clear circulating lactate. However, it appears that AS and AA were not matched according to physical activity that may interfere with the interpretation of their results. The greater activity recently found for the RBC monocarboxylate transporter, MCT-1, in AS could

Table 2. Parameters of the Bi-Exponential Curves Fitted to Blood Lactate Recovery Curves Obtained from the 1-min Supramaximal Cycling Exercise

		La(0) (mmol.L ⁻¹)	A ₁ (mmol.L ⁻¹)	γ ₁ (min ⁻¹)	A ₂ (mmol.L ⁻¹)	γ ₂ (min ⁻¹)
Groups	AS (n = 8)	4.68 ± 0.88	11.11 ± 1.34	0.31 ± 0.04	-14.40 ± 1.26	0.08 ± 0.02
	AA (n = 8)	3.83 ± 0.59	11.57 ± 2.45	0.33 ± 0.07	-13.93 ± 2.36	0.07 ± 0.01

Values are means ± SEM. A₁ and A₂ (amplitude terms of the two exponential time functions), γ₁ and γ₂ (velocity constants which denote the abilities to exchange and remove lactate, respectively), La(0) (venous blood lactate concentration at the end of the exercise), (n) number of subjects. No significant difference between the two groups.

Table 3. Parameters of the $\dot{V}O_2$ Recovery Kinetics Obtained from the 1-min Supramaximal Cycling Exercise

		$\dot{V}O_{2B}$ (ml.kg ⁻¹ .min ⁻¹)	A ₁ (ml.kg ⁻¹ .min ⁻¹)	τ ₁ (sec)	A ₂ (ml.kg ⁻¹ .min ⁻¹)	τ ₂ (sec)
Groups	AS (n = 6)	28.7 ± 1.9	-18.7 ± 2.5	24.7 ± 2.7	-6.7 ± 1.2	163.3 ± 23.5
	AA (n = 6)	31.7 ± 1.9	-18.4 ± 2.1	22.4 ± 3.4	-8.5 ± 1.2	141.5 ± 14.6

Values are means ± SEM. $\dot{V}O_{2B}$ (baseline $\dot{V}O_2$, i.e. $\dot{V}O_2$ at the end of exercise), A₁ and τ₁ (amplitude and time constant of the primary component), A₂ and τ₂ (amplitude and time constant of the slow component), (n) number of subjects. Technical problem with the breath-by-breath automated metabolic system deprived us from mathematical modelling of 2 AS and 2 AA. No significant difference between the two groups.

contribute to the better regulation of lactate exchange between blood and other cellular compartments [26]. However, the present study demonstrated that the ability to remove lactate was quite similar in the two groups as already suggested in another recent study using a different methodological approach to assess mechanisms of lactate metabolism regulation during exercise [27]. Therefore, the mechanisms involved in blood lactate regulation during exercise, such as RBC MCT-1, might be saturated or depressed during recovery, which would lead in turn to quite similar lactate recovery curves in the two groups.

No significant relationship was observed between γ₂ and A₂ (r = 0.04; P > 0.05) or between γ₂ and τ₂ (r = -0.44; P > 0.05) in the two groups altogether.

Several studies have investigated the relationship between [La] and the slow component of $\dot{V}O_2$ recovery kinetics [11-13, 20, 28]. Some of them suggested that lactate removal might have an effect on the recovery rate of oxygen consumption after strenuous exercise [12, 13, 20]. These authors estimated that during the slow component of $\dot{V}O_2$ recovery kinetics, 50% of lactate is oxidised while the other 50% is reconverted to glycogen. Thus, a causal and temporal relationship between EPOC and lactate kinetics has been reported [12]. However, we found no significant relationship between lactate removal ability and the slow component of EPOC in the present study, thereby reinforcing the conclusion previously drawn by Brooks and Gaesser [11], who had used the radioactive tracer technique to demonstrate the absence of a causal relationship between lactate and EPOC. Rose *et al.* [29] found, in the horse, that despite the presence of a correlation between the slow component of EPOC and pulmonary artery plasma lactate level, the $\dot{V}O_2$ returned to baseline by 20 min whereas blood lactate remained elevated. It is suggested that the mechanisms which result in elevated blood lactate may also be associated to the prolonged post exercise elevation of $\dot{V}O_2$ [20]. In addition, the resultant lactic acidosis following exercise may stimulate ventilation by its action on the arterial chemoreceptors and this increased ventilation might participate (but not fully explain) to the increased $\dot{V}O_2$ during

recovery. Other mechanisms have been proposed to explain the slow component of EPOC such as catecholamines and temperature [20, 28] but we did not address any of these factors in the present study.

Connes *et al.* [4] recently reported that AS were prone to exercise intolerance and lower aerobic capacity during prolonged submaximal exercise due to higher $\dot{V}O_2$ -on slow component. This excess of $\dot{V}O_2$ during exercise should have an effect on the subsequent $\dot{V}O_2$ recovery kinetics. However, the parameters describing the first and second components of the $\dot{V}O_2$ recovery kinetics did not differ between the two groups in the present study. Exercise intensity and duration are known to influence EPOC magnitude [13]. The exercise performed by AS and AA in the present study and in the study of Connes *et al.* [4] were very different and could explain this discrepancy.

The lack of significant difference in lactate removal ability and EPOC between the two groups is quite surprising if we take into account the recent study performed by Connes *et al.* [7] on the same participants and exercise protocol. The authors investigated the changes in blood rheology in response to exercise in AS and AA and found higher blood viscosity and lower RBC deformability at rest, at the end of the 1-min supramaximal exercise test, and during the following recovery period in AS [7]. Altered haemorheology is known to disturb blood circulation and therefore adequate O₂ delivery to tissues [30, 31], which should influence EPOC and lactate metabolism. However, recent reports also indicate that high blood viscosity could have a beneficial effect because of the stimulation of endothelial nitric oxide synthase by increasing shear stress and the subsequent vasodilatation [32-34]. Therefore, the different blood rheology profile found in AS [7] could favour greater vasodilatation providing normal O₂ delivery to tissues, which would ensure normal lactic response and normal $\dot{V}O_2$ recovery kinetics. Besides, Connes *et al.* [35] recently reported a significant positive correlation between the increase of blood viscosity during exercise and the enlargement of the arterio-venous oxygen content in athletes suggesting that the increase

of blood viscosity may contribute to the increase of oxygen consumption. Further studies are needed to fully explain these mechanisms.

The main limitation of the present study was the limited number of participants and the present findings should be considered as preliminary. Our results suggest that lactate removal ability and $\dot{V}O_2$ recovery kinetics were not different between AS and AA in response to a short supramaximal exercise test. The ability to recover after a short supramaximal exercise seemed to be not altered by sickle cell trait. Nevertheless, the presence of clinical sign should justify to prolong recovery or to stop exercise in AS because it has been reported that AS might be at greater risk for medical complication in response to exercise than AA [36]. The mechanisms responsible for these results are not fully understood and require further studies in larger cohort. Also, different short-term supramaximal exercise (longer duration, all-out) need to be investigated to confirm these preliminary results.

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