ARTICLE - Red Cell Biology & its Disorders

Endurance training improves oxygen uptake/demand mismatch, metabolic flexibility and recovery in patients with sickle cell disease

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Supplemental

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Mougin *et al.*

Supplemental information on the population of patients

None of the patients displayed severe complications including chronic inflammatory or infectious disease, kidney insufficiency, clinical signs and/or history of heart failure, left ventricular ejection fraction <50%, pulmonary arterial hypertension with tricuspid regurgitation velocity >2.8 m/s, atrial fibrillation, ventricular arrhythmias, left ventricular hypertrophy, significant valvulopathy, known coronary disease, uncontrolled hypertension, treatment with anti-arrhythmia drugs (including β-blockers), current anti-coagulant treatment, a pacemaker or defibrillator, known cerebral vasculopathy, prior stroke and epilepsy.

Supplemental results and discussion

The slope coefficient of the $\dot{V}O_2$ *vs.* W relationship has been reported to be lower in young adult and adult patients with SCD than in control subjects[1–3]. This lower slope coefficient likely results from lower muscle oxygen supply (due to anaemia, microvasculature rarefaction and low capillary/fibre surface of exchange) and/or lower muscle ability to consume oxygen (as testified by lower oxidative enzymes activity, lower peripheral extraction and arterialisation of venous blood) in SCD patients[4–6]. These results and inferences are in total accordance with a previous study performed in patients with COVID-19 for whom the observed lower slope coefficient of the $\dot{V}O_2$ *vs.* W relationship was concomitant to both lower arterial oxygen content and peripheral extraction during rest as well as exercise[7].

In the present study, we recorded elevated RER values during rest and low-intensity exercise. Firstly, as mentioned in the main text, this is not the first time that elevated RER values are reported in SCD patients[1,8–10]. Second, these values cannot be related to metabolic cart dysfunction. Indeed, to ensure validity of gas exchange measurements, the metabolic cart underwent standard service before the study and at mid experiments. Furthermore, the metabolic cart underwent successful calibration before each measurement session. Additionally, the experiments took place over 18 months, during which time values remained similar. Furthermore, it cannot be argued that data are related to unsteady states. Supplemental figure 1 shows clearly that a steady state in oxygen uptake is reached during the last 10 breathing cycles of each stage of the submaximal incremental tests (SIT1 and SIT2). This is actually not surprising. Indeed, the increment between two successive stages is so small (10 W for women and 15 W for men) that even if the stage duration is rather short (2 min), a steady state is reached. Along the same line of reasoning, the steady state being obtained before and after training it cannot be argued that the improvement of the slope coefficient is false/fake and related to an unsteady state before training and a steady state after training. In the aggregate, the proper functioning of the metabolic cart and the steady states obtained during the last 20 seconds of each stage during SIT1 and SIT2 argue in favor of the facts that i) the RER values were correct, strongly suggesting acid/base disturbances in patients with SCD, ii) the change of the slope coefficient was real and not due to unsteady states before training and steady states after training, and iii) when possible/appropriate, substrate partitioning calculation were reliable, strongly suggesting a predominantly carbohydrate utilization in patients with SCD.

The supplemental table 1 reports metabolic equivalent of task (MET) values for each patient during SIT1 as SIT2.

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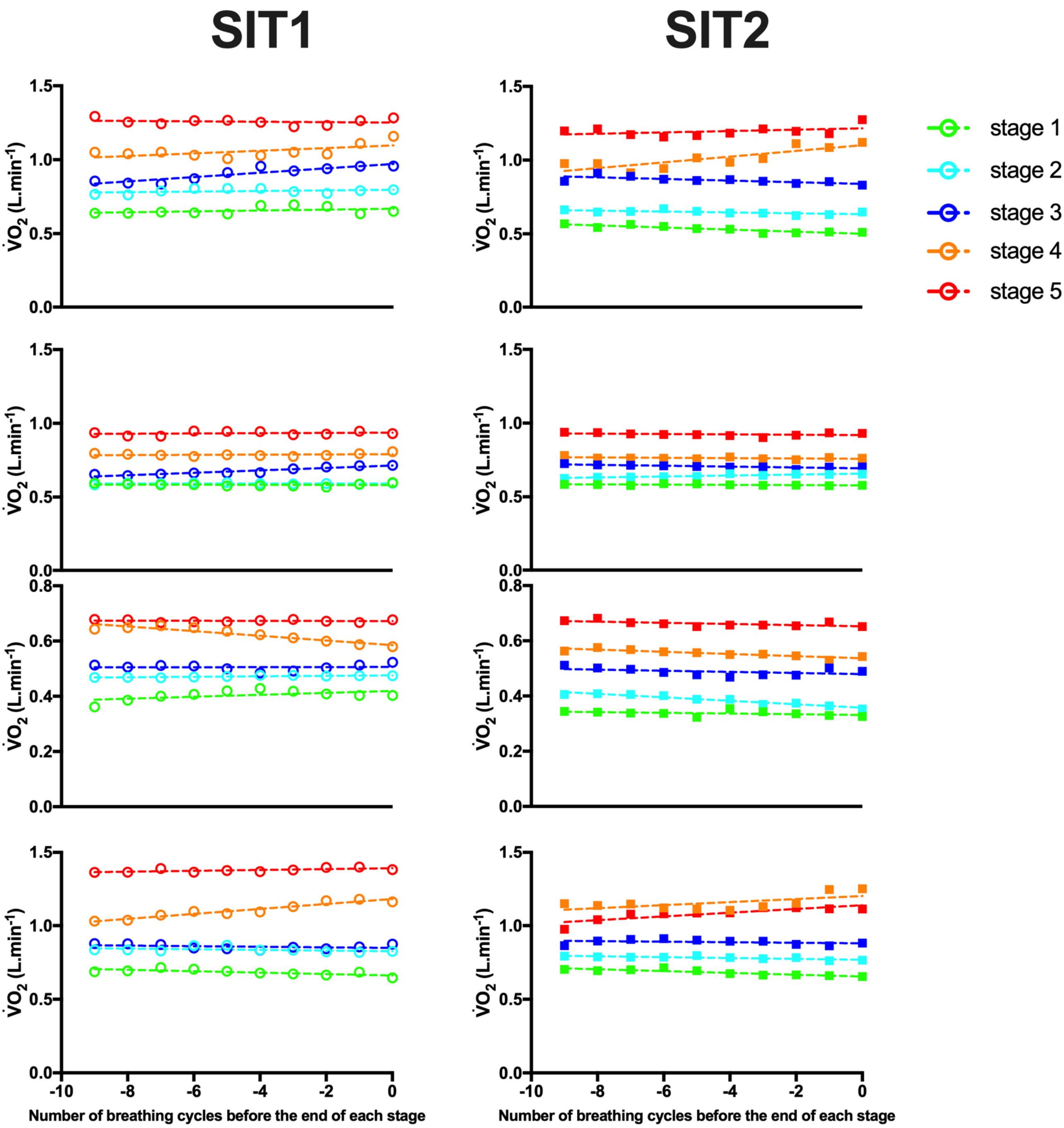
Supplemental table 1: Metabolic equivalent of task (MET) for each step of SIT1 and SIT2.

Males		30 W	45 W	60 W	75 W	90 W	105 W	120 W	135 W
1	SIT1	2.09	2.58	3.54	4.19	4.51			
	SIT2	2.74	3.18	3.74	4.19	4.95			
2	SIT1	2.36	4.02	3.95	4.32	4.75	5.95		
	SIT2	2.56	3.06	3.09	4.29	4.75	5.91		
3	SIT1	2.17	2.42	3.00					
	SIT2	1.63	2.24	2.71	*3.58*				
4	SIT1	1.72	2.77	3.24	3.95	4.45	*4.62*		
	SIT2	3.95	4.37	4.79	5.55	6.64	*6.60*		
5	SIT1	3.04	3.66	3.84	4.82	6.12			
	SIT2	2.72	3.53	3.93	5.00	*4.46*			
6	SIT1	2.65	3.35	4.04	4.24	*4.37*			
	SIT2	3.27	3.96	4.65	6.16	6.16			
7	SIT1	1.82	2.86	2.94	*3.55*				
	SIT2	2.99	3.72	4.55	5.54	5.54			
8	SIT1	2.37	3.35	3.67	4.04				
	SIT2	2.78	3.43	3.63	4.29	4.24	4.82	5.10	
Females		20 W	30 W	40 W	50 W	60 W	70 W	80 W	90 W
1	SIT1	1.78	2.20	2.34	2.95	3.19	3.23		
	SIT2	1.78	1.87	2.34	2.62	3.09	3.89	4.26	
2	SIT1	2.91	3.29	3.45	3.61	3.83	4.37	*4.91*	
	SIT2	2.16	2.53	3.29	3.56	4.26	4.64	5.07	5.23
3	SIT1	2.39	2.75	3.64	3.90	*4.42*			
	SIT2	2.55	2.86	3.27	4.00	*4.52*			
4	SIT1	2.55	2.62	2.86	2.62	3.10	3.34		
	SIT2	2.10	2.58	2.79	3.10	3.34	4.34	*4.72*	
5	SIT1	1.92	2.36	2.47	2.69				
	SIT2	2.42	2.58	2.75	3.35	*3.79*			
6	SIT1	3.38	3.44	3.91	4.49	5.42			
	SIT2	3.38	3.73	4.20	4.78	5.36			
7	SIT1	3.03	3.31	3.42	4.15				
	SIT2	2.91	3.31	3.75	4.31	4.59			

Values on the left hand side, in italic and grey were obtained at minute one of the two-minute stage.

Figure legends

Supplemental figure 1. Typical $\dot{V}O_2$ responses during the last 10 breathing cycles of each stage of SIT1 (before training, left panel) and SIT2 (after training, left panel) in four typical subjects (two males and two females). $\dot{V}O_2$ is a wavelet mean value over 5 seconds. SIT: submaximal incremental exercise test.



SIT1
SIT2
stage 1
stage 2
stage 3
stage 4
stage 5
V̇O₂ (L.min⁻¹)
Number of breathing cycles before the end of each stage