Cardiopulmonary adaptation and the acute phase inflammatory response to exercise in children and young adults with sickle cell anemia

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Although poor physical functioning is common among individuals with sickle cell anemia (SCA), the pathophysiologic contributors to exercise limitation are not clear in this population. We aim to examine the cardiopulmonary and acute phase response to maximal exercise testing in 37 children and young adults with SCA. Compared to controls, subjects with SCA demonstrated significant reductions in peak VO_2 and compromise in measures of ventilatory efficiency and oxygen delivery on gas exchange analysis. Exercise capacity correlated with biomarkers of hemolysis and inflammation. A biphasic acute phase inflammatory response to exercise was also suggested on kinetic profiling in subjects with SCA.
Keywords: Cardiopulmonary disease, Acute phase response, Exercise capacity, Sickle cell anemia

INTRODUCTION

Sickle cell anemia (SCA) is characterized by chronic pain, hemolytic anemia, cardiopulmonary disease and other complications that impact physical functioning, yet the exact pathophysiologic determinants of exercise limitation in these individuals are not well understood. Our objectives were to: 1) evaluate peak oxygen consumption (VO_2) and other aerobic parameters of the cardiopulmonary response to exercise in children and young adults with SCA, and 2) characterize the acute inflammatory response to exercise, as measured by an increase in soluble vascular cell adhesion molecule (sVCAM) activity and other biomarkers, in this population.

METHODS

We studied a convenience sample of non-transfused children and young adults with SCA (hemoglobin SS or S-β^0 thalassemia) at our institution. Subjects with SCA underwent symptom-limited cardiopulmonary exercise testing by cycle ergometry (Godfrey protocol) with workload ramping at 1-min increments until maximal effort was reached. Breath-by-breath, gas exchange analysis was performed with the SensorMedics Vmax metabolic cart. The relationship between exercise capacity and baseline biomarkers for hemolysis and inflammation was examined. We explored the kinetics of the acute phase response to exercise by sampling blood pre-exercise and at t=0, 30, 60 and 120 min after exercise. Statistical analysis was performed using SPSS V19.0.

RESULTS

Data from 37 subjects with SCA (mean age 15.5±3.3, range 9 to 21 years) and 10 race-matched controls without SCA (mean age 12.3±2.6, range 9 to 18 years) were analyzed. Of subjects with SCA, 89% had hemoglobin SS disease and 57% were male. There were no adverse events related to exercise testing. In total, 36/37 (97%) of subjects with SCA completed exercise testing with maximal effort, with termination of testing due to fatigue in all. Significant reductions in exercise capacity and anaerobic threshold were observed among subjects with SCA. Compared to controls, a greater proportion of subjects with SCA demonstrated peak VO2 < 80% predicted (87 vs. 40%, p = 0.006) and reduced anaerobic threshold (49 vs. 0%, p = 0.008). Mean total test time, peak VO_2 and peak VO_2/kg were also lower in subjects with SCA versus controls (Table I). Subjects with SCA demonstrated significant differences in measures of cardiopulmonary adaptation during maximal exercise testing. Breathing reserve was reduced in 7/32 (22%) subjects with diminished exercise capacity. Among all subjects with SCA, $\Delta V_E/\Delta VCO_2$ and V_E/VCO_2 at anaerobic threshold were higher compared to controls, suggesting compromise in ventilatory efficiency. Oxygen

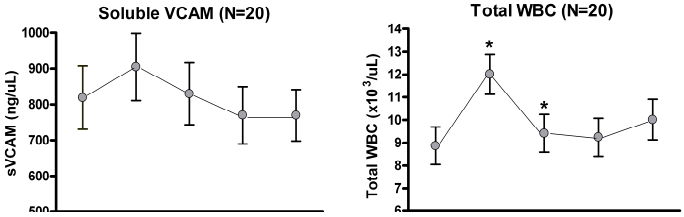
delivery during exercise, as reflected by $\Delta VO_2/\Delta WR$, was lower in subjects with SCA. There was no significant difference in $\Delta VO_2/\Delta HR$ between subjects with SCA and controls, indicating comparable oxygen pulse during exercise in the 2 groups.

Table I. Parameters on Cardiopulmonary Exercise Testing

	Subjects with SCA		Controls without SCA		
	Mean (±SD)	Range	Mean (±SD)	Range	*P* value
Test Time (min)	5.9±1.2	3.2 – 8.4	7.3±1.3	5.4 – 9.2	0.004*
Peak Work (watts)	116±36	43 – 202	141±47	54 – 193	0.080
Peak VO_2 (L/min)	1.5±0.4	0.9 – 2.6	2.2±0.6	1.1 – 3.1	0.009*
Peak VO_2/kg (ml/kg/min)	27.8±5.8	16.7 – 41.2	42.6±9.5	27.4 – 56.6	0.001*
Heart Rate Reserve (bpm)	23±33	-16 – 174	57±47	6 – 154	0.012*
Anaerobic Threshold (L/min)	1.15±0.28	0.59 – 1.90	1.91±0.53	1.05 – 2.85	0.001*
$\Delta V_E/\Delta VCO_2$ at AT	30.3±2.8	23.8 – 36.8	27.5±2.7	23.9 – 31.9	0.007*
$\Delta V_E/\Delta VCO_2$	30.6±3.1	21.2 – 38.7	27.1±2.5	23.6 – 31.3	0.002*
$\Delta VO_2/\Delta WR$ ($x10^{-3}$)	9.3±1.6	6.7 – 13.5	12.8±1.8	9.9 – 16.2	0.001*
$\Delta VO_2/\Delta HR$ ($x10^{-3}$)	10.7±4.9	1.4 – 20.2	10.9±10.6	0.78 – 27.4	0.966
Peak VD/VT	0.15±0.19	0 – 1.28	0.11±0.04	0.06 – 0.2	0.479

**P* value significant by unpaired student t-test; AT – anaerobic threshold; VD – dead space ventilation; VT – tidal volume

We examined the linear relationship of peak VO_2, peak VO_2/kg and peak work rate to biomarkers of hemolysis and inflammation. Pearson's correlation coefficients between peak VO_2/kg and biomarkers were strongest, specifically for baseline hemoglobin (r = 0.70, p = 0.0001), reticulocyte count (r = –0.62, p = 0.0001), total white blood cells (r = –0.54, p = 0.0001), absolute neutrophils (r = –0.49, p = 0.001) and D-dimer activity (r = –0.57, p = 0.0001). The acute phase inflammatory response to exercise was explored in 20 subjects with SCA. Mean sVCAM activity increased immediately after exercise with an increase of 85.5 ng/mL or 10.4% of baseline (Figure). We observed a dual peak in total white blood cells, neutrophils and monocytes and IL-6 activity characterized by an immediate rise after exercise at t = 0 min followed by a secondary increase at t = 120 min. Only changes from baseline in total white blood count at t = 0 min and IL-6 activity at t = 120 min after exercise were statistically significant.



CONCLUSIONS

Children and young adults with SCA demonstrate significant reductions in cardiopulmonary fitness on maximal exercise testing. The abnormal cardiopulmonary response to exercise in this population appears to be associated with compromise in ventilatory efficiency and oxygen delivery. Exercise limitation may also be explained in part by baseline hemolysis and greater inflammation. Although the kinetic profile is not fully elucidated, preliminary data suggest a biphasic acute phase inflammatory response to exercise in this population. Additional studies to examine the impact of exercise limitation on disease severity and prognosis are warranted.