Published in final edited form as:

J Pediatr Hematol Oncol. 2011 March ; 33(2): 93–97. doi:10.1097/MPH.0b013e318200ef49.

Attenuated Maximal Muscle Strength and Peak Power in Children with Sickle Cell Disease

Kelly A. Dougherty, Ph.D.¹, Joan I. Schall, Ph.D.¹, Alisha J. Rovner, Ph.D.³, Virginia A. Stallings, M.D.^{1,2}, and Babette S. Zemel, Ph.D.^{1,2}

¹Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA

²School of Medicine, University of Pennsylvania, Philadelphia, PA

³Eunice K Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

Abstract

Dominant hand maximal handgrip strength with a handgrip dynamometer and peak power with a force plate, adjusted for body size and composition were compared in 5- to 13-yr-old African-American children with and without type SS sickle cell disease (SCD-SS). Children with SCD-SS (n = 35, 9.0 ± 2.0 yrs) compared to healthy controls (n = 103, 8.6 ± 1.8 yrs) did not differ by age, gender, or pubertal status, yet had significantly lower Z scores for height, weight, body mass index, upper arm muscle area, upper arm fat area, fat and lean mass-for-height. Children with SCD-SS had significantly lower handgrip strength (12.7 ± 3.3 vs. 15.2 ± 5.1 kg, P < 0.008), peak power (882 ± 298 vs. 1167 ± 384 W, P < 0.001) and growth and body composition adjusted Z scores for handgrip strength (0.6 ± 1.3 standard deviations, P < 0.004) and peak power (males = 1.0 ± 0.8, P < 0.0002; females = 1.0 ± 1.7, P < 0.006). Maximal muscle strength and peak power are attenuated in children with SCD-SS compared to controls beyond expectation for growth and body composition deficits suggesting additional factors contribute to the attenuation in anaerobic performance.

Keywords

anaerobic performance; handgrip; force plate; growth; body composition

INTRODUCTION

Type SS sickle cell disease (SCD-SS) is a genetic disorder characterized by chronic hemolytic anemia and tissue damage due to repeated microvascular obstruction by sickle-shaped cells. Common vaso-occlusive triggers include red-cell dehydration, hypoxemia, metabolic acidosis and hyperthermia (10). Poor growth and nutritional status (3), increased protein turnover (8), reduced lean body mass, and elevated resting and lower activity energy expenditures (1;4) are often observed in children with SCD-SS. Taken together, these

Address for correspondence and reprints: Kelly A. Dougherty, Ph.D., Children's Hospital of Philadelphia, 3535 Market Street, Room 1556, Philadelphia, PA 19104 Phone: 215-590-2579 Fax: 215-590-0604 doughertyk@email.chop.edu.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

clinical findings present a conundrum for recommending participation in physical activities. Although exercise may put children with SCD-SS at risk for complications such as a “painful event”, not exercising deprives them of the salutary effects of regular physical activity, including accrual of lean body mass, strength and fitness.

Strong powerful muscles, which help to keep the skeleton in proper alignment, are essential for rapid movement in emergency situations and performing activities of daily living. Moreover, the physical activity patterns in which children engage, characterized by short bouts of rapid, high intensity movements interspersed with longer periods of low intensity motion (2), underscore the importance of developing adequate muscular strength and power throughout childhood. Of the few exercise studies comparing children with SCD-SS to healthy children, the majority focused on aerobic performance leaving a dearth of empirically-based information regarding anaerobic performance.

The purpose of this study was to examine maximal muscle strength and peak power in children with SCD-SS. It was hypothesized that compared to healthy controls, children with SCD-SS would have significantly reduced muscle strength and peak power even after adjustment for confounding variables such as body size and composition.

MATERIALS AND METHODS

Subjects

Subjects for this study were 5- to 13-yr-old African-American children with and without SCD-SS. SCD-SS subjects were recruited from the Comprehensive Sickle Cell Center at the Children's Hospital of Philadelphia (CHOP) and Division of Hematology at the Newark Beth Israel Medical Center for a vitamin A supplementation study. Baseline data from this study (prior to vitamin A supplementation) are presented. Healthy control subjects were a subset of children from the Reference Project on Skeletal Development in Children study, recruited from the CHOP primary care practices and surrounding community. Exclusion criteria for subjects with SCD-SS included chronic blood transfusion therapy, acute transfusion within last two months, liver enzymes above three times the reference range, history of stroke, hydroxyurea therapy, not in steady state of health (including fever or pain event within two weeks), weight or height > 97th percentile for age and sex (14), serum retinol > 30 µg/dl, or other chronic medical conditions known to affect growth, dietary intake or nutritional status. Control subjects' exclusion criteria were any disease, genetic syndrome or use of medication known to affect growth, nutritional status, or bone health, and weight or height > 97th percentile for age and sex (14). Verbal assent was given by the child and written informed consent was provided by the parent / guardian. This study was approved by the CHOP Institutional Review Board.

Anthropometry and body composition

Anthropometric measurements obtained in triplicate followed standardized techniques (17) and the mean used for analysis. Body mass index (BMI) was calculated (kg/m^2) from weight using a digital scale (Scaletronix, White Plains, NY) and standing height using a stadiometer (Holtain, Crymych, UK). Weight, height and BMI were compared to Centers for Disease Control and Prevention 2000 reference standards to generate age- and gender-specific Z scores (14). Measurements of mid-upper arm circumference with a non-stretchable fiberglass tape (McCoy, Maryland Heights, MO) and triceps skinfold thickness with a skinfold caliper (Holtain, Crymych, UK) were used to calculate upper arm muscle and fat areas. Resultant areas were compared to African-American reference data from the National Center for Health Statistics to generate Z scores (11). Total body fat and lean body mass were measured by whole body dual energy X-ray absorptiometry (DXA; Hologic

4500A, Bedford, MA) and compared to the Reference Project on Skeletal Development in Children data to generate race and gender specific DXA Z scores for lean body mass and fat mass relative to height.

Maturation and hematologic parameters

Pubertal status according to the criteria of Tanner (24) was determined using a validated self-assessment questionnaire (20). Subjects with SCD-SS had measurements of hemoglobin, fetal hemoglobin and hematocrit using standard techniques.

Maximal muscle strength and power

Maximal handgrip strength of the right and left hand was measured with a handgrip dynamometer (Takei, Tokyo, Japan). Hand dominance was determined by asking which hand was used to hold a pencil. The subject stood upright with the shoulder adducted holding the dynamometer, not touching the trunk. The handle was adjusted to the child's hand size and no extraneous body movement was allowed during testing. For each hand, three maximal effort trials lasting 4- to 5-seconds interspersed with 60-second rests were performed and the highest dominant hand value retained for analysis.

Peak power was calculated from the force-time curve and velocity of the center of mass during a maximal vertical squat jump using a Kistler Quattro Jump Portable Force Plate System (Model 9290AD, Amherst, NY). Before testing, subjects completed a 5-min treadmill warm-up, walking at a comfortable speed at 0% grade. Subjects completed three warm-up followed by three maximal vertical jumps from an initial static squat position with knees at 90° flexion and arms akimbo and the highest value was used for analysis.

Statistical analyses

All variables were tested for normality and nonparametric tests were used as appropriate. Group differences were determined using either a Student's *t*-test or Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables. Multivariate regression models were constructed for subjects in the control group using a multistage approach to assess effects of fat mass, lean body mass, height, age and gender on maximal muscle strength and peak power. Based upon results of preliminary regression models, to account for the effect of gender, multivariate regression models for peak power were constructed separately for males and females in the control group. Selection of variables for final models was based on statistical significance, maximum R^2 values, and distribution of residuals. These results were used to create prediction models to calculate Z scores for children with SCD-SS. All statistical analyses were performed using STATA 9.0 (College Station, TX), results considered significant at $P < 0.05$, and data presented as means $\pm$ SD.

RESULTS

Forty-eight children with SCD-SS and 106 controls were evaluated. Analyses were restricted to the 35 children with SCD-SS (16 female) and 103 controls (48 female) with complete data. Twenty-nine children with SCD-SS and 87 controls were classified as Tanner stage 1 and 6 children with SCD-SS and 16 controls were stage 2. Subject characteristics are presented in Table 1. There were no group differences for age, gender or pubertal status. Compared to controls, children with SCD-SS were similar in height but had significantly lower weight and BMI. Overall, growth status was suboptimal in children with SCD-SS indicated by negative Z scores for height, weight and BMI. Nutritional status, demonstrated by arm circumference, triceps skinfold thickness, upper arm muscle and fat areas, and associated Z scores, was suboptimal in SCD-SS compared to controls. Children with SCD-

SS had significantly lower lean body and fat mass in kilograms and associated Z scores relative to height, compared to controls.

All hematologic measures reflected the SCD diagnosis, with reduced hemoglobin concentrations (8.1 ± 0.9 mg / dL), hematocrit ($23.6 \pm 3.1\%$) and elevated fetal hemoglobin production ($9.0 \pm 5.9\%$).

Children with SCD-SS had significantly lower dominant hand maximal handgrip strength (SCD-SS = 12.7 ± 3.3 vs. controls = 15.2 ± 5.1 kg, $P < 0.008$) compared to controls. Lean body mass, fat mass and age were significant predictors of dominant hand maximal handgrip strength in control subjects, together explaining 76% of the variance (Table 2). Compared to controls, dominant hand maximal handgrip strength Z scores for children with SCD-SS were significantly lower, by 0.6 ± 1.3 standard deviations ($P < 0.004$).

Compared to controls, children with SCD-SS had significantly lower peak power (SCD-SS = 882 ± 298 vs. controls = 1167 ± 384 W, $P < 0.001$). Based upon results of preliminary regression models in controls, separate multivariate regression models for peak power were constructed for males and females (Table 3). Lean body mass and age for both males and females were significant predictors of peak power, in addition to a trend for height for females. Collectively, these variables explained 83 and 90% of the variance in control males and females, respectively. Compared to controls, peak power Z scores for children with SCD-SS were significantly lower, by 1.0 ± 0.8 and 1.0 ± 1.7 standard deviations, for both males ($P < 0.0002$) and females ($P < 0.006$), respectively.

Peak power Z scores were positively associated with fetal hemoglobin, a measure of disease severity in children with SCD-SS ($r = 0.40$, $P < 0.03$). No performance measures were associated with either hematocrit or hemoglobin concentrations.

DISCUSSION

We found that children with SCD-SS compared to healthy children of similar age, race and pubertal status had attenuated lean body mass, dominant hand maximal handgrip strength and peak power and group differences persisted when measures were adjusted for body size and composition. This highlights the importance of improving growth status, body composition and nutritional status in children with SCD-SS and suggests additional factors contributed to reduced anaerobic performance.

Muscle strength, the maximal amount of force exerted in a single muscle contraction, reflects tension from actin sliding past myosin filaments within muscle fibrils. A main determinant of muscle strength is muscle size; the larger the muscle the greater the contractile force generated. After birth the number of muscle fibers remains relatively constant and increases in muscle bulk reflects muscle hypertrophy. Muscle strength also increases as a child grows paralleling hypertrophy of muscle fibers. Our study showed diminished lean body mass in children with SCD-SS compared to controls. Although Moheeb et al. (19) found a significant deficit in grip strength and “explosive power” via a vertical jump apparatus in children with SCD-SS vs. healthy peers, values were not adjusted for deficits in body size or composition. Our results agree and extend these findings to show that group differences were not explained by body size and composition deficits suggesting additional factors contributed to lower strength and power in children with SCD-SS.

Due to the invasive nature of the procedures, few studies have investigated size-independent variables accounting for improvements in muscle strength with age in healthy children, with no studies conducted in children with SCD-SS. Possible candidates in healthy children include changes in innervation, muscle architecture and muscle contractile properties with

growth (6;12;15;21). Upper extremities nerve conduction velocity increases with age in children and may be related to thinning of the distal compared to proximal portions of the axons as limbs grow in length (15). In adults the rate of maximal motor unit discharge, which declines with age and corresponds to the decline in muscle strength, may limit force production (21). No information on intramuscular needle electrodes is available in children. Changes in motor unit recruitment patterns with age could affect metabolic and physiologic exercise response; however no prospective investigations exist in children. Comparing force-versus-time relationships during single muscle contraction in children and adults, Going et al. (12) showed maximal rate of force production and time to reach maximal force were lower in children indicating changes in muscle contractile properties occur with normal growth. Lastly, muscle angle of pennation changes as a child grows (6) possibly affect strength development. Either alone or in concert, any of these variables could affect changing patterns of muscular force production during growth in children. In the present study, it is unknown if these factors contributed to attenuated muscle strength in children with SCD-SS compared to their healthy peers, and more research is warranted.

Limited data from healthy subjects suggest genetics, muscle fiber differentiation and contractile properties, and motor unit recruitment and activation are possible factors affecting peak power during growth (5;9;16;18;23). Studies demonstrating similarities in short-term power in twins (18) and siblings but not adopted brothers and sisters (23), indicate that genetic factors likely contribute to observed differences, possibly accounting for up to half of the variance in anaerobic power. The percent distribution of type II (fast-twitch) muscle fibers, recruited for high-power activities, increases with age in children (9) possibly affecting performance in short-burst activities. As type II fibers have a greater maximum shortening velocity than type I fibers (16), this might alter the velocity-dependent measures of force and power. Lastly, Belanger and McComas using the interpolated twitch technique in 10- to 16-yr-old boys showed the degree of motor unit activation of knee extensors during extreme effort varied by age (5) and speculated improved motor coordination likely contributed to gains in muscle force. Thus, it is probable that size-independent factors contribute to development of peak power during childhood. In the present study, it is unclear if any of these variables contributed to the lower peak power measures in children with SCD-SS compared to their healthy counterparts, and more research is needed.

In the present study, peak power Z scores positively correlated with fetal hemoglobin (disease severity) in children with SCD-SS. No child was prescribed hydroxyurea a medication that increases fetal hemoglobin production (7). In adults with sickle cell anemia, hydroxyurea therapy significantly improved peak power (13). Future studies to determine if hydroxyurea administration improves anaerobic performance in children with SCD-SS are needed.

Limitations

This sample may not be representative of children with SCD-SS since they were recruited for a suboptimal vitamin A status study. However, this is common identified in 66% screened (22). Also, vitamin A status did not correlate with performance measures (data not shown).

In summary, even after adjusting for body size and composition, maximal muscle strength and peak power are attenuated in children with SCD-SS compared to healthy children. This highlights the importance of improving growth status, body composition and nutritional status in children with SCD-SS and suggests that additional factors contribute to the attenuation in anaerobic performance.

Acknowledgments

The authors are grateful to the children and their families for study participation. Also, we thank the Clinical Translational Research Center (UL1-RR-024134), CHOP Nutrition Center, CHOP Comprehensive Sickle Cell Center, Director Kwaku Ohene-Frempong, Division of Hematology at Newark Beth Israel Medical Center, Director Wondwesson Bekele, M.D., and Deborah Kawchak.

Supported by Comprehensive Sickle Cell Center (NIH 5 U54 HL070596), Clinical Translational Research Center (UL1-RR-024134) and CHOP Nutrition and Growth Laboratory.

Reference List

1. Akohoue SA, Shankar S, Milne GL, et al. Energy expenditure, inflammation, and oxidative stress in steady-state adolescents with sickle cell anemia. *Pediatr Res*. 2007; 61:233–238. [PubMed: 17237728]
2. Bailey RC, Olson J, Pepper SL, et al. The level and tempo of children's physical activities: an observational study. *Med Sci Sports Exerc*. 1995; 27:1033–1041. [PubMed: 7564970]
3. Barden EM, Kawchak DA, Ohene-Frempong K, et al. Body composition in children with sickle cell disease. *Am J Clin Nutr*. 2002; 76:218–225. [PubMed: 12081838]
4. Barden EM, Zemel BS, Kawchak DA, et al. Total and resting energy expenditure in children with sickle cell disease. *J Pediatr*. 2000; 136:73–79. [PubMed: 10636978]
5. Belanger AY, McComas AJ. Extent of motor unit activation during effort. *J Appl Physiol*. 1981; 51:1131–1135. [PubMed: 7298453]
6. Binzoni T, Bianchi S, Hanquinet S, et al. Human gastrocnemius medialis pennation angle as a function of age: from newborn to the elderly. *J Physiol Anthropol Appl Human Sci*. 2001; 20:293–298.
7. Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med*. 2008; 148:932–938. [PubMed: 18458271]
8. Buchowski MS, de la Fuente FA, Flakoll PJ, et al. Increased bone turnover is associated with protein and energy metabolism in adolescents with sickle cell anemia. *Am J Physiol Endocrinol Metab*. 2001; 280:E518–E527. [PubMed: 11171608]
9. Colling-Saltin, AS. Skeletal muscle development in the human fetus and during childhood. In: Berg, K.; Eriksson, BO., editors. *Children and Exercise IX*. University Park Press; Baltimore: 1980. p. 193–207.
10. de Montalembert M. Management of sickle cell disease. *BMJ*. 2008; 337:a1397. [PubMed: 18779222]
11. Frisancho, AR. Anthropometric standards for assessment of growth and nutritional status. University of Michigan Press; Ann Arbor: 1990.
12. Going SB, Massey BH, Hoshizaki TB, et al. Maximal voluntary static strength production characteristics of skeletal muscle in children 8–11 years of age. *Res Q Exerc Sport*. 1987; 58:115–123.
13. Hackney AC, Hezier W, Gullledge TP, et al. Effects of hydroxyurea administration on the body weight, body composition and exercise performance of patients with sickle-cell anaemia. *Clin Sci (Lond)*. 1997; 92:481–486. [PubMed: 9176021]
14. Kuczmarski, RJ.; Ogden, CL.; Grummer-Strawn, LM., et al. CDC Growth Charts: United States. National Center for Health Statistics; Hyattsville, MD: 2000. p. 1–28.
15. Lang HA, Puusa A, Hynninen P, et al. Evolution of nerve conduction velocity in later childhood and adolescence. *Muscle Nerve*. 1985; 8:38–43. [PubMed: 4058457]
16. Larsson L, Moss RL. Maximum velocity of shortening in relation to myosin isoform composition in single fibres from human skeletal muscles. *J Physiol*. 1993; 472:595–614. [PubMed: 8145163]
17. Lohman, TG.; Roche, AR.; Martorell, R. Anthropometric standardization reference manual. Human Kinetics; Champaign: 1988.
18. Malina RM, Mueller WH. Genetic and environmental influences on the strength and motor performance of Philadelphia school children. *Hum Biol*. 1981; 53:163–179. [PubMed: 7239495]

19. Moheeb H, Wali YA, El Sayed MS. Physical fitness indices and anthropometrics profiles in schoolchildren with sickle cell trait/disease. *Am J Hematol*. 2007; 82:91–97. [PubMed: 16986131]
20. Morris NM, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. *J Youth Adolesc*. 1980; 9:271–280.
21. Patten C, Kamen G, Rowland DM. Adaptations in maximal motor unit discharge rate to strength training in young and older adults. *Muscle Nerve*. 2001; 24:542–550. [PubMed: 11268027]
22. Schall JJ, Zemel BS, Kawchak DA, et al. Vitamin A status, hospitalizations, and other outcomes in young children with sickle cell disease. *J Pediatr*. 2004; 145:99–106. [PubMed: 15238915]
23. Simoneau, JA.; Lortie, G.; Leblach, C., et al. Anaerobic alactacid work capacity in adopted and biological siblings. In: Malina, RM.; Bouchard, C., editors. *Sport and Human Genetics*. Human Kinetics; Champaign: 1986. p. 165-171.
24. Tanner, JM. *Growth at Adolescence*. Blackwell Science; Oxford: 1962. The development of the reproductive system; p. 28-39.

Table 1

Subject Characteristics

	Controls (n=103)	SCD-SS (n=35)	P-value
Age, yr	8.6 ± 1.8	9.0 ± 2.2	0.20
<i>Growth status</i>			
Height, cm	133.4 ± 12.0	129.7 ± 11.1	0.11
Height Z score	0.5 ± 1.0	-0.5 ± 0.9	0.001
Weight, kg	34.0 ± 11.0	26.7 ± 5.7	0.003
Weight Z score	0.8 ± 1.1	-0.7 ± 0.9	0.001
BMI	18.7 ± 3.9	15.7 ± 1.3	0.001
BMI Z score	0.7 ± 1.1	-0.5 ± 0.8	0.001
<i>Anthropometry</i>			
Arm circumference, cm	21.9 ± 3.7	18.1 ± 2.0	0.001
Arm circumference Z score	0.9 ± 1.4	-1.0 ± 0.9	0.001
Triceps skinfold thickness, mm	12.3 ± 5.2	7.4 ± 2.1	0.001
Triceps skinfold thickness Z score	0.4 ± 1.2	-0.8 ± 0.7	0.001
UAMA, cm ²	26.4 ± 7.7	20.1 ± 4.4	0.001
UAMA Z score	1.1 ± 1.5	-0.6 ± 1.0	0.001
UAFA, cm ²	12.9 ± 7.3	6.4 ± 2.1	0.001
UAFA Z score	0.7 ± 1.5	-0.9 ± 0.6	0.001
<i>Body composition determined by DXA</i>			
LBM, kg	24.6 ± 6.3	20.8 ± 4.6	0.002
LBM-for-height Z score	0.0 ± 1.0	-1.3 ± 1.0	0.001
FM, kg	8.8 ± 5.7	5.2 ± 1.5	0.001
FM-for-height Z score	0.2 ± 1.1	-0.2 ± 0.7	0.02

SCD-SS, type SS sickle cell disease; BMI, body mass index; UAMA, upper arm muscle area; UAFA, upper arm fat area; LBM, lean body mass; FM, fat mass.

Table 2
Multivariate regression models predicting dominant hand maximal handgrip strength for healthy control children.

	Coefficient (kg)	Standard error	t	P-value	R ²
Healthy control (n = 103)					
Lean body mass, kg	0.6	0.1	6.3	0.001	0.76
Fat mass, kg	-0.2	0.1	-3.4	0.001	
Age, yr	0.9	0.3	3.8	0.001	
Constant	-5.3	1.2	-4.4	0.001	

Table 3

Multivariate regression models predicting peak power for healthy control male and female children.

	Coefficient (W)	Standard error	t	P-value	R ²
Healthy control males (n = 55)					0.83
Lean body mass, kg	41.5	5.5	7.6	0.001	
Age, yr	71.7	18.6	3.9	0.001	
Constant	-477.2	112.2	-4.25	0.001	
Healthy control females (n = 48)					0.90
Lean body mass, kg	56.0	5.7	9.9	0.001	
Age, yr	56.1	22.3	2.5	0.02	
Height, cm	-7.6	3.9	-1.9	0.06	
Constant	339.9	313.3	1.1	0.28	