Heart Rate Recovery Is Impaired after Maximal Exercise Testing in Children with Sickle Cell Anemia

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Objective To examine heart rate recovery (HRR) as an indicator of autonomic nervous system dysfunction after maximal exercise testing in children and young adults with sickle cell anemia (SCA).

Study design Recovery phase heart rate (HR) in the first 5 minutes after maximal exercise testing in 60 subjects with SCA and 30 matched controls without SCA was assessed. The difference between peak HR and HR at both 1-minute (ΔHR_{1min}) and 2-minutes recovery was our primary outcome.

Results Compared with controls, subjects with SCA demonstrated significantly smaller mean ΔHR_{1min} (23 beats per minute [bpm], 95% CI 20-26 vs 32 bpm, 95% CI 26-37, $P = .006$) and the difference between maximal HR and HR at 2 minutes (39 bpm, 95% CI 36-43 vs 48 bpm, 95% CI 42-53, $P = .011$). Subjects with SCA also showed smaller mean changes in HR from peak HR to 1 minute, from 1 minute to 2 minutes, and from 2 through 5 minutes of recovery by repeated-measures testing. In a multivariable regression model, older age was independently associated with smaller ΔHR_{1min} in subjects with SCA. Cardiopulmonary fitness and hydroxyurea use, however, were not independent predictors of ΔHR_{1min}.

Conclusions Children with SCA demonstrate impaired HRR after maximal exercise. Reduced postexercise HRR in SCA suggests impaired parasympathetic function, which may become progressively worse with age, in this population. *(J Pediatr 2015;166:389-93)*.

Impaired heart rate recovery (HRR) after exercise, particularly at the 1- and 2-minute intervals, is an indicator of autonomic nervous system (ANS) dysfunction and represents a prognostic indicator of future cardiovascular morbidity and mortality in the general population.[1,2] A delayed decrease in heart rate (HR) measured in the first minute of recovery serves as a predictor of death independent of myocardial perfusion defects on nuclear imaging or HR response during exercise.[1] Decreased exercise capacity also is associated with abnormal HRR in both men and women.[1] Normal HRR at 1-minute after exercise has been shown to be vagally mediated, reflecting early parasympathetic reactivation rather than sympathetic withdrawal.[3]

Cardiovascular ANS dysfunction, primarily from impaired vagal function, also exists among individuals with both sickle cell anemia (SCA) and sickle cell trait. Sickle cell trait carriers exhibit altered sympathovagal balance both at rest and after exercise.[4] In SCA, transient hypoxia produced changes in HR variability in young adults with SCA but not in controls without SCA, indicating substantial parasympathetic withdrawal in response to oxygen desaturation.[5] Moreover, individuals with SCA demonstrate poor cardiopulmonary fitness resulting in decreased physical functioning and reduced exercise capacity.[6,7] Potential causes for reduced exercise capacity in SCA include chronic anemia, cardiopulmonary disease, deconditioning, and a proinflammatory state. However, the exact physiological mechanisms and factors responsible for exercise limitation in this population remain poorly understood. Whether autonomic dysfunction in patients with SCA is a function of low fitness is not known.

We hypothesized that after maximal cardiopulmonary exercise testing, children and young adults with SCA demonstrate reduced HRR compared with individuals without SCA. We also hypothesized that reduced HRR is associated with poor cardiopulmonary fitness and other clinical variables in this cohort.

ΔHR_{1min}	Difference between peak HR and HR at 1 minute
ANS	Autonomic nervous system
bpm	Beats per minute
ECG	Electrocardiogram
HR	Heart rate
HRR	Heart rate recovery
SCA	Sickle cell anemia
VO_2	Oxygen consumption
WBC	White blood cell

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Funded by the National Institutes of Health/National Heart, Lung, and Blood Institute (K23 HL094376). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.10.064

Methods

We analyzed HR data obtained during the recovery phase of maximal cardiopulmonary exercise testing in a cohort of children and young adults with SCA enrolled in a prospective study aimed at characterizing the physiologic determinants of exercise limitation in this population. This study was approved by the Institutional Review Board of Ann & Robert H. Lurie Children's Hospital of Chicago. Complete informed consent and assent were obtained where appropriate from all participants and their parents before they began study activities.

Subjects were approached during routine visits and recruited from the Comprehensive Sickle Cell Program. We included subjects between 8 and 21 years of age with hemoglobin SS or $S^{-}\beta^{0}$ thalassemia confirmed by routine hemoglobin analysis. Individuals receiving hydroxyurea therapy were eligible for participation. Subjects were excluded for the following: (1) participation in chronic transfusion program; (2) history of cardiovascular disease or significant chronic lung disease; or (3) history of lightheadedness, syncope, or chest pain with physical exertion. Controls without SCA or sickle cell trait were recruited from siblings or relatives of subjects enrolled in this study, other patients seen in clinic, or from study advertisements placed in the clinic and hospital settings. Absence of SCA or trait was verified by hemoglobin analysis or confirmation of newborn state screen results. Controls were matched by age, sex, and race.

All subjects and controls underwent incremental, symptom-limited, maximal cardiopulmonary exercise testing at steady state. Steady state in subjects with SCA was defined by the absence of vaso-occlusive pain or other sickle cell–related complication for at least 2 weeks or the absence of any transfusion for at least 3 months before testing. We followed a standard ramp cycle protocol (modified Godfrey protocol[8]) using an electronically braked VIAsprint 150P/200P cycle ergometer (CareFusion Corporation, San Diego, California). Initial workload and increments in workload every 1 minute (ie, work rate) were determined by subject height. Continuous breath-by-breath gas exchange and 12-lead electrocardiogram (ECG) data were monitored during exercise. After a maximal exercise test, defined as reaching a respiratory exchange ratio equal to or greater than 1.1, participants engaged in a 10-minute recovery phase. During recovery, each individual continued to pedal on the cycle ergometer without resistance at a cadence of 40-60 rpm for the first 3 minutes and then remained in a sitting position after getting off the cycle. Peak oxygen consumption (VO_2) was determined by choosing the greatest 20-second averaged, weight-adjusted VO_2 achieved during the last minute of exercise. Exercise testing was discontinued if the study participant requested to stop because of excessive fatigue; developed sickle cell related pain; experienced symptoms of severe shortness of breath, palpitations, cyanosis, or dizziness; or exhibited significant decrease in oxygen saturation with worsening respiratory symptoms.

We analyzed tracings of postexercise ECG data recorded during the first 5 minutes of the recovery period and measured HR at 1-minute intervals. We limited our analysis to the first 5 minutes of recovery given the lack of uniform data collection across subjects and controls after 5 minutes. After standardized training, 2 research assistants used regular calipers to manually perform all measurements in leads II, V5, and V6. HR was determined by measuring the distance between consecutive RR intervals. Final HR values reflected the average of 3 independent measurements. HR reserve was calculated as the difference between peak HR and baseline HR.

Statistical Analyses

Summary statistics were used to report frequency and to evaluate distribution of all continuous data (SPSS v22.0; IBM Corporation, Armonk, New York). The difference between peak HR and HR at 1 minute (ΔHR_{1min}) and 2 minutes of recovery represented our primary outcome. Continuous variables were compared using Student t test for independent samples between subjects and controls or ANOVA among subjects on hydroxyurea, subjects not on hydroxyurea, and controls. Post hoc Bonferroni comparisons were performed for significant results found on ANOVA testing. Repeated-measures ANOVA was used to evaluate group effect on HR change at 1 minute, from 1 to 2 minutes, and through 5 minutes of recovery. We performed multivariable linear regression to assess the association between clinical variables and ΔHR_{1min} in 2 separate models, one for subjects with SCA and controls without SCA combined and another for subjects with SCA only. Clinical variables included age, sex, peak VO_2, baseline hemoglobin, baseline white blood cell (WBC) count, and hydroxyurea use (subjects only). HRR time constants were calculated via standard exponential equations and displayed as monoexponential curves. Results at 95% CI with two-tailed, $P < .05$ were considered statistically significant.

Results

Baseline and postexercise HR data were assessed in 60 subjects with SCA and 30 matched controls without SCA. Postexercise ECG data could not be interpreted because of excessive motion artifact in 2 subjects. Therefore, the final cohort consisted of 58 subjects (mean age 15.1 years, 95% CI 14.2-16.0) and 30 controls (mean age 14.5 years, 95% CI 13.3-15.8). In total, 30/58 (52%) and 15/30 (50%) of subjects and controls were male, respectively, and 22/58 (38%) subjects were receiving hydroxyurea treatment at the time of testing. Mean HR at baseline was significantly greater for subjects with SCA compared with controls without SCA (78 beats per minute [bpm], 95% CI 76-81 vs 71 bpm, 95% CI 66-76, $P = .005$) (Table I).

We analyzed ECG tracings at the end of exercise and the beginning of the recovery phase to determine peak HR responses to maximal exercise testing. There was no significant difference in the mean peak HR achieved during maximal