

Erythrocyte Sickling During Exercise and Thermal Stress

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Objective: To examine effects of exercise in the heat and fluid intake on erythrocyte sickling and neutrophil activation in carriers of sickle cell trait (HbAS).

Design, Setting, and Participants: Six African American men (2 HbAS; 42% HbS, 4 HbAA; 20.7 ± 0.8 years; 87.4 ± 9.6 kg) participated in 2 randomized sessions (separate days) each consisting of 45 minutes of brisk walking (treadmill) in a hot (33°C) environment.

Intervention: Subjects consumed no fluids or fluid for 3 hours prior to (ad libitum) and during (1.02 L) testing.

Main Outcome Measurements: Core temperature, heart rate, and perceived exertion were measured. Forearm venous blood was analyzed for percent erythrocyte sickling and plasma myeloperoxidase.

Results: Time-averaged heart rate (126.6 ± 5.7 vs. 146.7 ± 5.9 bpm; $P = 0.02$) and core temperature (37.6 ± 0.1 vs. 38.1 ± 0.1°C; $P < 0.05$) responses were lower during fluid versus no fluid, with no statistically significant difference in perceived exertion (12.3 ± 0.5 vs. 13.6 ± 0.4; $P = 0.06$). Erythrocyte sickling progressively increased (to 3.5%–5.5%) for HbAS carriers during no fluid exercise only. No sickling was detected in HbAA subjects. Plasma myeloperoxidase responses to exercise were greater ($P = 0.03$) in HbAS versus HbAA.

Conclusions: Fluid ingestion at a rate sufficient to offset a body weight deficit can effectively reduce erythrocyte sickling during exercise in the heat.

Key Words: sickle cell trait, hydration, myeloperoxidase

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INTRODUCTION

Sickle cell trait has been characterized as a benign disorder,¹ with little or no risk of sickling in vivo.² Accordingly, sickle cell trait is often not considered to be a restriction to

athletic participation,³ a detriment to exercise performance,⁴ or an independent factor to increase exercise risk.⁵ However, Kark et al⁶ indicated a 30-fold greater rate of unexplained exercise-related sudden death among black recruits with sickle cell trait compared with black recruits without hemoglobin S. A number of fatal and nonfatal events (e.g., nonfatal exertional collapse, heat illness, and rhabdomyolysis) have also been reported with recruits, athletes, firefighters, and children.^{7–9}

A combination of extensive exercise, dehydration, and thermal strain may be enough to induce sufficient hyperthermia, hyperosmolality, acidosis, and red cell dehydration, potentially leading to significant erythrocyte sickling, inflammation, microvascular occlusion, and ultimately to exertional collapse and exercise-induced sudden death in certain HbAS carriers.^{7,8,10} However, few reports on exertional-related death or life-threatening complications among HbAS carriers noted field hydration status or core body temperature⁸; therefore, the contribution of each is unclear.

We examined whether a low level of progressive sickling would occur in healthy volunteers with sickle cell trait in response to exercise and thermal stress. We also investigated whether improved hydration would lower metabolic stress and core body temperature during exercise in the heat, and thus reduce or eliminate any exercise-induced changes in erythrocyte sickling and acute signs of neutrophil activation.

METHODS

Six African American men (2 HbAS; 42% HbS, 4 normal hemoglobin [HbAA]; 20.7 ± 0.8 years; 87.4 ± 9.6 kg) participated in 2 randomized sessions (2–7 days apart), consisting of 45 minutes of walking (treadmill) in a hot environment (33°C; 45% relative humidity). For 1 session, subjects consumed no fluids (NF) for 3 hours prior to or during testing. For the other, subjects were encouraged to drink (ad libitum) non-caffeine fluids (F) throughout the morning and up to the exercise session. During F, subjects consumed water (170 mL) at the start of exercise and every 10 minutes thereafter (total, 1.02 L). This rate of fluid ingestion offset sweat-induced fluid losses during F, so that there was no body weight deficit at the end of exercise. The institutional Human Assurance Committee approved the study, and subjects provided written informed consent prior to participation.

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Exercise Intensity

During familiarization (FAM) sessions (1 week earlier), treadmill speed and elevation were adjusted so that the subjects were walking briskly, eliciting a rating of perceived exertion (RPE: Borg category ratio scale) of 13 to 15 (somewhat hard to hard) for most of the 45-minute exercise period. Subjects consumed no fluids for 3 hours prior to or during the FAM exercise session (same as during NF). For the subsequent randomized F and NF sessions, the same exercise protocol and work rate (from the FAM sessions) were used for each individual. Heart rate (bpm) was continuously monitored using a Polar® monitor (Polar Electro Inc., Woodbury, NY).

Blood Collection and Analyses

Blood was collected (20-gauge catheter, antecubital vein) at the following times: pre, pre-exercise; 15 minutes, at 15 minutes; 30 minutes, at 30 minutes; IP, immediate postexercise; and 15 minutes post, after 15 minutes of standing cool-down in 22°C. For percent sickling, whole blood was drawn into EDTA tubes. The red cells were washed in saline, fixed in glutaraldehyde, and applied to a microscope slide. Slides were read on a Nikon Labophot, 2 phase-contrast microscope, in a blind, random order by an experienced hematologist. Ten fields of 100 erythrocytes each were examined, and sickled cells were counted and expressed as a percentage of total cells. Plasma from each original blood sample was separated and recentrifuged at 10,000 rpm to remove platelets and aggregates, then frozen at -80°C until assayed. Plasma myeloperoxidase (MPO) was measured by ELISA (OxisResearch, Portland, OR).

Core Temperature

Core temperature (°C) was monitored via ingestible telemetry sensors and a programmable hand-held monitor (HQ, Inc., Palmetto, FL). Each temperature sensor was ingested 5 hours prior to exercise.

Statistics

Data are reported as means \pm SEMs. The influences of sickle trait and fluid status were investigated by 2-factor, repeated-measures analysis of variance using Statview statistical software (SAS Institute, Cary, NC).

RESULTS

Time averaged heart rate (126.6 ± 5.7 vs. 146.7 ± 5.9 bpm; $P = 0.02$) and core temperature (37.6 ± 0.1 vs. 38.1 ± 0.1 °C; $P < 0.05$) were lower during and after (15 minutes – 15 minutes post) F compared with NF. RPE tended to be higher during (15 minutes – IP) NF (13.6 ± 0.4 vs. 12.3 ± 0.5 ; $P = 0.06$). Urine specific gravity indicated better ($P < 0.05$) pre-exercise hydration levels for F (1.017 ± 0.003) compared with

NF (1.024 ± 0.003). Only unequivocally sickled (not merely distorted or crenated) cells were counted (Fig. 1). No sickling was detected in the HbAA subjects.

Myeloperoxidase increased in response to exercise ($P < 0.001$); however, hydration had no statistical effect ($P > 0.05$). Therefore, we collapsed the hydration groups (NF and F) together and plotted the response in plasma MPO (Fig. 2), displaying HbAS versus HbAA. Neutrophil activation, indicated by MPO responses to exercise, was greater ($P = 0.03$) in the HbAS group.

DISCUSSION

In a hot environment without fluid intake, there was progressive sickling with only 45 minutes of brisk walking. However, improved hydration effectively lowered metabolic stress and core body temperature, essentially eliminating any exercise-induced changes in erythrocyte sickling.

In the event of sickling, changes in erythrocyte structure activate the complement cascade, which in turn can activate neutrophils to release MPO. Alternatively, neutrophils may become activated by direct contact with sickled red cells. Activated neutrophils (in addition to sickled erythrocytes) can adhere to endothelium, leading to further restriction in microvascular flow. In our study, those with HbAS had greater apparent exercise-induced neutrophil activation, but the MPO data do not support a conclusion that it was a response related to sickling alone.

CONCLUSION

Many athletes with HbAS regularly participate in demanding exercise without appreciating that they may be at particular risk. Our findings suggest that fluid ingestion at a rate sufficient to offset a body weight deficit can be a simple yet effective preventative strategy to reduce erythrocyte sickling during exercise in the heat.

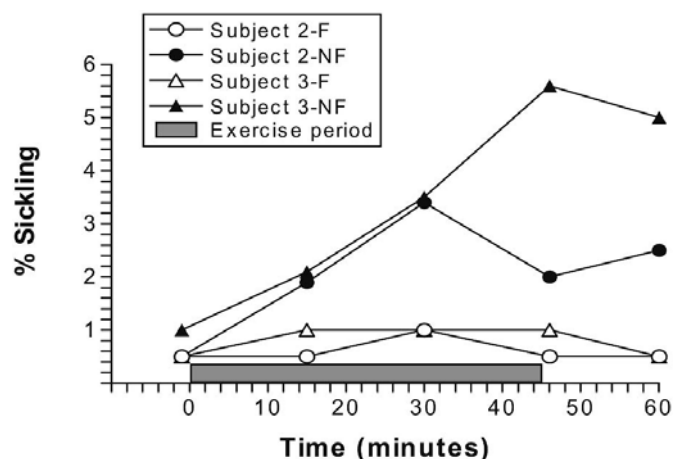


FIGURE 1. Percent (%) red blood cell sickling for the sickle cell trait (HbAS) carriers for NF and F trials.

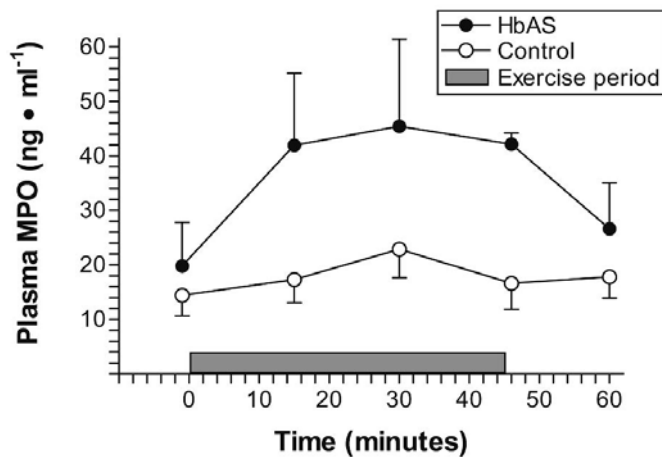


FIGURE 2. Plasma myeloperoxidase (MPO) responses for sickle cell trait (HbAS) carriers and control (HbAA) subjects with NF and F trials collapsed together. Neutrophil activation, indicated by MPO responses to exercise, was greater ($P = 0.03$) in the HbAS carriers.

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