CLINICAL SCIENCES

Scientific Summit Meeting Report

ACSM and CHAMP Summit on Sickle Cell Trait: Mitigating Risks for Warfighters and Athletes

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ABSTRACT

O'CONNOR, F. G., M. F. BERGERON, J. CANTRELL, P. CONNES, K. G. HARMON, E. IVY, J. KARK, D. KLOSSNER, P. LISMAN, B. K. MEYERS, K. O BRIEN, K. OHENE-FREMPONG, A. A. THOMPSON, J. WHITEHEAD, AND P. A. DEUSTER. ACSM and CHAMP Summit on Sickle Cell Trait: Mitigating Risks for Warfighters and Athletes. *Med. Sci. Sports Exerc.*, Vol. 44, No. 11, pp. 2045–2056, 2012. **Introduction**: An estimated 300 million people worldwide have sickle cell trait (SCT). Although largely benign, SCT has been associated with exertional rhabdomyolysis and exercise-related sudden death in warfighters/athletes (WA). The National Collegiate Athletic Association's policy to confirm a student athlete's SCT status during their preparticipation medical examination prompted reaction from some organizations regarding the rationale and ethical justification of the policy. **Methods**: On September 26 and 27, 2011, a summit, composed of military and civilian experts in sports medicine and SCT, was convened at the Uniformed Services University in Bethesda, MD. The expert panel was charged with two objectives: 1) to provide specific recommendations to further mitigate the apparent risk with strenuous exercise in WA with SCT and 2) to develop clinical guidelines to identify, treat, and return to duty/play WA suspected to have incurred nonfatal sickle cell collapse. **Results**: New terminology is introduced, areas of current controversy are explored, consensus recommendations for mitigating risk and managing the WA with SCT are reviewed, and important areas for future research are identified. **Conclusion**: Further research is needed before conclusions can be drawn regarding the etiology of the increased death rate observed in WA with SCT, and the possibility exists that SCT is a surrogate for as yet another contributing factor for the unexplained deaths. **Key Words:** ATHLETIC HEALTH, EXERCISE COLLAPSE, HEMOGLOBINOPATHIES, RISK MANAGEMENT

Sickle cell trait (SCT) and its association to exertional rhabdomyolysis (ER) and exercise-related death (ED) in athletes are significant and controversial issues confronting the sports medicine community and the US Department of Defense (DoD) (33,52,91). Approximately 300 million people worldwide and nearly 9% of African Americans in the United States (approximately 3 million individuals) have SCT (48). The condition is largely benign, because complications are uncommon and typically mild (52). Two SCT-associated

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Submitted for publication June 2012.
Accepted for publication June 2012.

0195-9131/12/4411-2045/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e31826851c2

deaths in the military in 2010 and a 2010 National Collegiate Athletic Association (NCAA) policy requiring student athletes to provide documentation of their SCT status or sign a written release before beginning athletics activity have heightened attention and debate on the relationship between SCT and risk for both ER and ED.

The 2010 NCAA new policy and guidance on SCT were developed in response to student athlete deaths that were seemingly due to complications from SCT. This policy has raised national attention on the association between SCT and ED and the merits and ethical concerns of screening (52). The American Society of Hematology (ASH) issued a statement in 2012 strongly recommending that the NCAA reverse its policy; ASH cited a lack of scientific evidence to support SCT screening (38). Furthermore, the hematology society strongly endorsed evidence for universal precautions and guidelines to diminish exercise-related injuries and death, which could benefit all athletes, regardless of SCT status.

Each military service mandates its own policy. The U.S. Army does not screen for SCT but rather mitigates risk through policy-promoting universal precautions for all soldiers—careful attention to hydration, progressive heat acclimatization, and graduated conditioning and training. Whereas these interventions demonstrated reduced risk of exercise-related SCT complications, ED continues to sporadically occur in soldiers who are SCT positive (and negative). The death of two soldiers in 2010 prompted convening a summit and expert panel, in collaboration with the American College of Sports Medicine (ACSM), interested DoD entities, the American Medical Society for Sports Medicine (AMSSM), ASH, and selected members of the sports medicine community to discuss SCT, with particular emphasis on mitigating risk in warfighters and athletes (WA). This review reflects the discussions and debates that occurred during the conference. Specifically, we introduce new terminology, explore areas of current controversy, review recommendations for mitigating risk and managing WA with SCT, and identify vital areas for future research.

METHODS AND APPROACH

On September 26 and 27, 2011, the Consortium for Health and Military Performance (CHAMP) convened a summit and expert panel at the Uniformed Services University in Bethesda, MD. Participants included scientists and physicians from the DoD, representatives from ACSM, AMSSM, and NCAA, and other subject matter experts from ASH and the sports medicine and international research communities. The group was charged with two objectives: 1) to provide physical training and other specific recommendations to further mitigate the apparent risk with strenuous exercise in WA with SCT and 2) to develop clinical guidelines for primary care responders to identify, treat, and return to duty/play (RTDP) WA suspected to have incurred nonfatal sickle cell collapse during exercise. The expert panel reviewed SCT fatalities in military and civilian populations, current military and civilian policies and recommendations for WA with SCT, strategies for managing the collapsed WA with SCT, and future research needs.

DEFINITION AND DIAGNOSIS OF SCT

Normal adult hemoglobin (Hb) is composed of two α and two β chains, which come together to form the tetramer HbA. A mutation in the sixth codon that results in the substitution of valine for glutamic acid as the sixth amino acid in the β globin produces HbS. A person with SCT inherits a β-A gene from one parent and a β-S gene from the other, allowing both HbA and HbS to be produced in each red blood cell (RBC). Persons with SCT always have more HbA than HbS, which is also called AS (implying more A than S). In contrast, those with sickle cell disease (SCD) inherit the β-S gene from both parents and produce no HbA in their RBCs—only HbS or SS.

A definitive diagnosis of SCT can be made by one of two methods: Hb separation and quantitation methods or analysis of β-globin genes. The presence of HbA and HbS in RBCs, with HbA predominating in a person who has not received an RBC transfusion in three or more months, establishes SCT. Currently, more than 1100 Hb variants exist and many share common charge and migration characteristics; so more than one method (e.g., electrophoresis, isoelectric focusing, and various chromatographic methods) may be required for correct identification.

Simple tests that determine the mere presence of HbS are of limited use and fraught with false-negative results. Currently, the most common "sickling test" is the solubility test (Sickledex). It relies on the relative insolubility of deoxyhemoglobin S in an aqueous solution and is usually positive (i.e., HbS present) in both SCT and all types of SCD. The results can be false negative when the relative proportion of fetal Hb is high, hematocrit <26, SCT and α-thalassemia trait are present (see the effects of α-thalassemia on Hb S percentages in SCT carriers in Table 1), or SCT is concomitant with iron deficiency anemia. In addition, Hb solubility and RBC sickling tests fail to detect other common Hb variants, such as HbC, D, or E. A "negative" solubility test does not mean a person is "normal" and that he/she cannot produce a child with SCD. Studies evaluating the solubility test in people "between 5 and 40 yr" of age have demonstrated a false-positive rate of 0% and false-negative rate of 1% (45).

TABLE 1. Common α-thalassemia syndromes and their effect on percentage HbS in SCT.

α Genes Deleted	Genotype	Clinical Phenotype	HbS (% ± SD)
0	Normal ($\alpha\ \alpha/\alpha\ \alpha$)	Normal	37.1 ± 2.51*
1	Heterozygous α thal ($-\ \alpha/\alpha\ \alpha$)	Silent carrier—normal hematologic profile	32.6 ± 1.91*
2	Homozygous α thal ($-\ \alpha/-\ \alpha$) or heterozygous α^0 thal ($-\ -/\alpha\ \alpha$)	A thalassemia trait—mild microcytic anemia	25.5 ± 1.44*

ATHLETIC PERFORMANCE WITH SCT

Since the 1980s, epidemiological and laboratory studies have characterized the physiological responses to exercise in persons with SCT. Notably, SCT does not appear to limit participation in various sports under elite performance demands. In the Ivory Coast, the prevalence of SCT in competitors running the Abidjan semimarathon was the same as in that general population (56). Similar results have been found in runners of the International Mount Cameroon Ascent Race in Cameroon (84), and some Olympic sprinters have been SCT carriers (61,69).

Brief single-bout, power-reliant performance. A large epidemiological study between 1956 and 1995 indicated that a higher percentage of Ivory Coast track and field throw and jump champions were SCT carriers compared with the general population. Accordingly, one might speculate that SCT contributes to success in very brief and explosive track and field events involving mainly alactic energy metabolism (10) or with limited reliance on anaerobic glycolysis. The 34 (27.8%) SCT carriers identified across the 122 national champions won 78 national titles (24.5%) and established 37 national records (43.5%) among the throw and jump events (10). Notably, the women's high jump and men's shot-put record holders had the highest percentages of SCT carriers—90.9% and 87.5%, respectively. Importantly, SCT carriers have been shown to achieve superior performance during jump-and-reach tests compared with non-SCT controls (46). Whereas a potential underlying mechanism has yet to be identified, a 2010 study reported SCT carriers tended to have a higher cross-sectional surface area of Type IIx fibers—the muscle fibers recruited during brief, single explosive movements (94).

Anaerobic performance. Le Gallais et al. (55) analyzed exercise performance in SCT carriers during National Ivory Coast athletic sports events and found SCT carriers established 32/33 national records for distances under 400 m. Similar to jumping and throwing, SCT carriers may have a greater ability to excel in short and intense running than that in longer distance events and have the capacity to safely tolerate and train for short-distance competitions. However, laboratory studies on anaerobic power and circulating lactate levels have not demonstrated significant differences between SCT carriers and control groups (9,22).

In contrast, the ability of SCT carriers to perform repeated, short bouts of anaerobic-predominant exercise, with limited recovery between bouts, may be lower than that of non-SCT carriers (22). Hypothetically, the capacity to rapidly recover from such exercise bouts could be compromised in SCT carriers because of the reliance on a rapid rate of oxygen delivery and use after each repeated bout (23). However, excess postexercise oxygen consumption after 1-min bouts of short supramaximal exercise at 110% maximal oxygen uptake ($\dot{V}O_{2max}$) did not differ between SCT carriers and controls (21). These data suggest that exercise recovery is not compromised in SCT carriers (21), but a larger sample size would be needed to confirm or refute these preliminary findings.

Aerobic performance. Individuals with SCT are not selectively excluded from participation in aerobic sports/activities (54); however, epidemiological investigations from the Ivory Coast (55,56) indicate SCT might limit reaching a high level of performance during activities relying on sustained aerobic metabolism. Comparisons of $\dot{V}O_{2max}$ (gold standard for aerobic fitness) between SCT carriers and non-SCT controls yielded no differences (62,75,77), even under acute mild, moderate, or severe hypoxic conditions (63,97–99). When SCT carriers and non-SCT controls were compared on other criteria of aerobic fitness (ventilatory threshold and lactate threshold), no differences existed between the two populations (39,60,66). Similarly, when SCT carriers and controls repeated three incremental exercise bouts to exhaustion, interspaced with 10 min of recovery, no differences in any cardiorespiratory parameters were detected (60). However, Vincent et al. (94) found lower cytochrome C oxidase activity in muscle fibers from SCT carriers relative to controls, which could limit oxidative energy metabolism and lower aerobic capacity in this population (23).

EXERCISE COLLAPSE ASSOCIATED WITH SCT

The summit revealed that clinical presentations within the military and sports medicine community for WA with SCT were unique from those reportedly seen among clinical hematologists in persons with SCD. In particular, fulminant ER and severe muscle pain, weakness and/or cramping presentations appear to be uniquely distinct from the characteristic painful crises identified in SCD patient populations. However, several reports (58,59,83) describe myonecrosis in the context of a sickle cell vaso-occlusive crisis, which suggests this may be an overlooked and underdiagnosed consequence (18). After considerable debate, the group collectively agreed that the clinical presentations observed in WA with SCT would be identified as "exercise collapse associated with SCT" or ECAST.

Clinical presentation of ECAST. ECAST appears to be a spectrum presentation in WA with SCT because it varies from severe muscle pain to fulminant collapse (33). Although ECAST has been noted in both military and sport settings at various levels of training/conditioning and competition, American football conditioning appears to account for the majority of ECAST events (40). In football conditioning, the proximate trigger for ECAST appears to be high-intensity exercise (30,33). The typical setting reported for precipitation of ECAST is an athlete near maximal exertion—repeated or sustained—for a short time. Of the 10 Division I football players with SCT who died in the past decade, five had been doing serial sprints for 5 to 30 min and four had been doing fast-tempo, multistation drills, with little or no rest between stations, for 12 to 60 min. In five of the earlier football players with SCT who died, sprinting for only 2–5 min reportedly led to ECAST (two players had newly arrived at altitude). ECAST can seemingly occur after finishing an hour-long, fast-tempo

TABLE 2. Common features reported for ECAST.

- Muscle weakness exceeds muscle pain, unlike heat cramping.
- Victim slumps to ground, unlike with sudden cardiac arrest or hobble of heat cramping.
- Victim can talk at first, unlike the unconscious state resulting from life-threatening arrhythmias seen in sudden cardiac arrest.
- Muscles look and feel normal to observer, unlike "locked up" muscles observed with heat cramping.
- Rapid tachypnea from lactic acidosis—but moving air well, unlike an asthma attack.
- Rectal temperature usually <103°F, uncommonly >106°F, as in exertional heat stroke.

station drill or after being on-field only briefly—for example, sprinting "all-out" for only 2–5 min (30,33).

A review of case reports revealed that typical training settings include the following: day 1 of conditioning, newly arrived at altitude, just returning from a vacation, or a sudden increase in the intensity of a conditioning drill (3). All ECAST events appear to involve a "perfect storm" of high-intensity exercise, sustained for at least a few minutes, and a "heroic effort" beyond what may be the physical limits of the athlete on that particular day (Table 2). The principal differential diagnosis in the struggling WA includes muscle cramps and collapse from heat illness, in addition to ECAST. The usual findings with exertional muscle cramps are painful, hard contracted muscles, whereas ECAST may be typified by pain, weakness, and flaccid or soft muscles (33). Those persons experiencing exertional heat illness (EHI) may present with ataxic gait, headache, decreasing performance, and eventually mental status changes, although the aforementioned are not commonly seen in the SCT WA with an ECAST event.

Epidemiology of ECAST: the civilian experience. A recent cohort study during a 5-yr period from 2004 to 2008 reported five NCAA ED events in SCT African American athletes (40). Harmon et al. (40) noted a 15-fold increased risk of ED for athletes with SCT compared with those without SCT, with all SCT deaths having occurred in Division I football players. African Americans with SCT in this Division I cohort had an ED risk of 1:827—a relative risk approximately 37 times greater than for African American Division I football players without SCT. However, ECAST is not exclusive to collegiate football players because the medical literature and lay press have reported its occurrence in high school athletes and athletes engaged in other strenuous physical activities (30,33,78,85), such as boxing (44). However, the full scope of the problem is difficult to glean from case reports alone. Deaths related to ECAST have been examined and underscored; however, the morbidity of ECAST remains unappreciated (30), because no case-control studies documenting these phenomena or incidence rates have been conducted (33).

Epidemiology of ECAST: the military experience. The military published a sentinel study supporting ECAST scenarios, prompted by the first known reports in the late 1960s when SCT carrier recruits died in basic training (47,50,65). Basic training involves rapid and sustained exercises for many conditioning activities, intense and focused military-specific training, and testing for 1- to 3-mile run times. Kark et al. (49–51) measured the excess risk of ED associated with SCT for Armed Forces recruits in basic training from 1977 to 1991, and subsequent studies provided mortality rates for recruits for a 25-yr period (29,49,51,79). Overall, the Armed Forces recruit studies indicated SCT was not associated with trauma, suicide, natural death unrelated to exercise (mainly infections), or deaths from preexisting disease (principally hidden congenital cardiovascular disease) (50,79). However, SCT was associated with unexplained (by preexisting disease) ED. The major findings were that unexplained ED rates among black recruits with SCT were 30 times higher than among black recruits without SCT and 39 times higher than all recruits (50,51).

In military populations who had completed basic training, Gardner et al. (36) found a much lower risk of unexplained ED with SCT. For example, no such cases were found among 200 episodes of unexplained ED over several years of army duty, and rates of unexplained ED among recruits in advanced training were very low (36). The very low residual risk, for those who passed entry-level basic training, might be explained by the elimination of a vulnerable subset of recruits, the removal of the unique and novel stresses to succeed during basic training, and/or protection conferred by sustained enhanced fitness and environmental acclimation.

IS SCT AN INDEPENDENT RISK FACTOR FOR ECAST?

The initial pathophysiological mechanisms of vaso-occlusion in SCD seem to involve several key interacting factors, such as impaired blood rheology (5), a proinflammatory vascular environment with abnormally adherent sickle cells, neutrophils and monocytes (42,71), coagulation abnormalities (53), and endothelial dysfunction (37). Increased hematocrit and blood viscosity are risk factors for vaso-occlusive crises (70,72), and RBC deformability gradually becomes impaired when a vaso-occlusive crisis develops (6).

Similarly to SCD, blood rheology and inflammatory factors have also been suggested as precipitating factors in ECAST in those with SCT (20). As such, several investigations have monitored these biological factors in response to exercise. To date, the main findings include the following: 1) SCT carriers at rest have increased blood viscosity (19,86,90), slightly decreased RBC deformability (19,87), somewhat increased RBC disaggregation threshold (87), and increased plasma concentration of the adhesion molecule vascular cell adhesion molecule 1 (4,67,68); 2) exercise results in a greater decrease in RBC deformability in SCT carriers than that in controls during late exercise recovery (89), but adequate hydration normalizes the hemorheological abnormalities of SCT carriers (90); 3) exercise results in a greater activation of leucocytes and platelets in SCT carriers than that in non-SCT controls (88); and 4) SCT carriers and controls exhibit very few differences in coagulation processes (7,24,100).

A recent study compared changes in biochemical markers reflective of muscle lysis in response to prolonged, moderate

cycling exercise in SCT carriers and non-SCT controls (64). Despite a greater blood viscosity in SCT carriers (90), serum creatine kinase and lactate dehydrogenase were similar in the two groups and remained unchanged in response to exercise. Both groups had increases in creatinine, Na^+, K^+, Cl^-, and myoglobin concentrations during exercise, although the changes were of the same magnitude (64). Unfortunately, the exercise performed in this study (64) was probably of insufficient intensity or duration to ascertain whether SCT carriers are at greater risk for ER than noncarriers. Accordingly, these data only indicate that SCT carriers can perform prolonged, moderate exercise without indications of consequent muscle damage.

Although most of the reported blood rheological alterations in SCT carriers are likely subclinical (86), 25% to 33% have true blood hyperviscosity. In fact, blood viscosity values may reach levels often observed in patients with HbSC disease (86,90). Indeed, it is unclear why more medical events are not reported in SCT carriers. Muscle biopsy data obtained by Vincent et al. (93) noted that SCT carriers had a lower capillary density and tortuosity, reduced numbers of small microvessels (diameter <5 mm), and a higher percentage of broader microvessels (diameter >10 mm) than noncarriers. Microvascular remodeling in SCT may serve to compensate for the blood hyperviscosity and thus facilitate a normal flow of RBCs through muscle tissues.

Collectively, these findings suggest that SCT carriers could be at a greater risk during or after certain exercise scenarios and conditions of microcirculatory alterations (16,17), which might lead to acute ischemic episodes in skeletal muscle cells.

Do other factors promote RBC sickling and vascular dysfunction? Several other contributing factors have been proposed as potentially increasing the risk for adverse events in SCT carriers. These include 1) exercise in heat and/or high humidity; 2) dehydration; 3) exercise at altitude; 4) exercise-induced asthma; 5) preexercise fatigue due to illness (e.g., viral infection) or lack of sleep (41); 6) poor conditioning (4); 7) high exercise intensity (33); and 8) dietary supplements containing stimulants (12,32). Except for high altitude (63,80) and heat exposure (16,43,50), hydration status (8,49,90), and poor conditioning (4), the potential contributions of the other factors to initiating adverse events in SCT carriers remain hypothetical. Importantly, the aforementioned risk factors for adverse outcomes also apply to those who are not SCT carriers, with the exception of altitude.

Chirico et al. (15) recently demonstrated that the oxidative stress response of exercising sedentary SCT carriers was greater than seen in exercising, physically trained SCT carriers. They concluded that being physically fit might decrease endothelial activation in SCT carriers through improvements in both nitric oxide and antioxidant availability (15), which could presumably limit the risk for ECAST. Accordingly, the risk of unexplained ED would likewise be lower after completing a season of competitive sport or basic training for military service compared with the risk upon program entry (15).

An alternate hypothesis is that HbS is a surrogate for or acts in combination with other gene variants to precipitate EHI or ER. Polymorphisms associated with the β-globin gene could account for some of the excess risk, especially if these variants served in some way to decrease the chance of surviving a severe episode of EHI. Other gene defects, such as variants in the ryanodine type 1 receptor (RYR1) may predispose individuals to ER (13,76). Future studies of unexplained exertional death cases with SCT should include screening for other genetic variants, as well as quantification of Hb variant distribution; this would help clarify the individual events.

ECAST CONTROVERSIES

To what extent do RBCs sickle during exercise? Although RBCs from persons with SCT can be induced to sickle *in vitro* (73), the extent to which they sickle *in vivo* is less clear. The Hb population in RBCs from persons with SCT (assuming minimal Hb F and normal HbA2) exists mostly in three forms: A, S, and a hybrid of α/β-A and α/β-S, designated as A/S (74). Unlike HbA, HbS and HbA/S hybrids both participate in polymer formation when deoxygenated; but with sufficient amounts of HbA (HbA > HbS), polymerization is inhibited to the extent that SCT RBCs do not sickle under most physiological conditions (1). Only under extreme physiological conditions—high plasma osmolarity, severe acidosis, and/or hypoxia—would polymerization of deoxy-HbS, sickling, and other related vascular dysfunction occur in some tissues of SCT individuals.

Few investigators have examined the percentage of sickle RBCs in SCT carriers during or after exercise (8,27,63,74,88). Among them, Martin et al. (63) tested the effects of acute hypoxia (1270 and 4000 m) on exercise performance and sickling rate. They demonstrated that maximal arm cranking exercise under light to severe hypoxia increased sickling of RBCs in SCT carriers: from 1.0% ± 1.0% at rest to 2.3% ± 2.6% during peak exercise at 1270 m and from 1.5% ± 12% to 8.5% ± 7.1% at 4000 m. However, sickling was highly variable, and oxygen consumption did not differ between SCT carriers and controls. Bergeron et al. (8) demonstrated progressive RBC sickling (3.5%–5.5%) in SCT carriers during exercise in the heat when hydration was restricted but not when hydration status was maintained. In these studies, the increases in RBC sickling did not appear to be clinically significant; however, these findings reinforce the suspicion that exercise-induced sickling and consequent vascular dysfunction may occur during exercise under certain conditions in WA with SCT.

ECAST and sickling: culprit or postmortem event? A key issue in the debate on SCT collapse is the absence of documented sickling as the initiator of an ECAST event. The causal relationship between SCT and exercise death is difficult to prove in a way that would fully support the hypothesis that fulminant sickling prompts these fatal events (3,57). Widespread multiorgan, small-vessel sickling can only be observed

on postmortem evaluation and thus cannot be assigned as the definitive cause of death or the consequence of determinant metabolic changes before death until more support for this cascade of events is documented (51). Accordingly, that progressive sickling is involved in these scenarios leading to death remains a viable hypothesis.

ECAST RISK MITIGATION: HEAT, HYDRATION, OR INTENSITY?

To date, no well-controlled, hypothesis-driven, prospective studies have examined SCT and exertional collapse in association with ECAST. However, the principal emphasis and efforts directed at ECAST risk mitigation have focused on controlling heat exposure, supporting adequate hydration, and addressing exercise intensity.

Heat. The military, in particular, the U.S. Army, focused on heat exposure and strain mitigation, as a result of prior epidemiological interventions (82). Kark et al. (49) demonstrated that ECAST-like incidents in the military recruit population were effectively mitigated by enforcing strategies to prevent EHI. Between 1982 and 1991, an intervention group (30,000 regular military recruits with SCT and 1.8 million without SCT) and a nonintervention group (Control Center: 13,500 recruits with SCT and 960,000 without SCT) were followed (51). Trainers in the intervention group conducted hourly monitoring of the wet bulb globe temperature (WGBT), so exercise intensity could be reduced and rest breaks increased as WGBT rose. Water intake, directly observed by trainers, went up as WGBT increased. Clothing was modified as WGBT levels rose to allow for increased evaporative and convective cooling. Immediate cooling and rehydration were provided for recruits who had difficulty keeping up with or "fell out" of training events.

No recruits with SCT from the intervention group died, whereas six recruits without SCT did (51). In contrast, 14 unexplained EDs were noted at Control Centers: 4 with SCT and 10 without SCT. A significant reduction in unexplained ED rates was noted for all recruits in the Intervention versus Control Centers, and unexplained ED rates for SCT recruits were 17-fold lower at Intervention than at Control Centers. In comparison with historical controls, SCT-related unexplained ED rates declined by at least 22-fold at Test Centers but only decreased 1.15-fold at Control Centers (51). These data imply that improved prevention of EHI can eliminate nearly all the excess mortality potentially associated with SCT. This study avoided biases by accurate collection of all deaths among a well-defined population with full recovery of population unexplained EDs and full autopsy, toxicology, clinical, and training data for 95% of deaths. It is important to note, however, that the army has not eliminated SCT deaths, as evidenced by the deaths that prompted this summit. Factors that may contribute to continued SCT deaths include but are not limited to lack of complete compliance with EHI prevention standards, medications, medical conditions, such as subclinical cardiac abnormalities, and the emerging role of dietary supplements. Thus, it is difficult to definitively evaluate the effectiveness of the army's approach.

Hydration. Several studies have examined the effect of hydration on RBC sickling or blood rheology during exercise (8). As noted above, Bergeron et al. (8) investigated the effects of brisk walking for 45 min in a hot environment on RBC sickling in SCT carriers. They demonstrated that sickling remained low and essentially unchanged by exercise when subjects were adequately hydrated. These findings are in contrast to a 2010 study where SCT carriers participated in 40 min of moderate cycling exercise (*not* in the heat) under two conditions: *ad libitum* hydration and water deprivation. Although some significant differences in blood rheology were demonstrated under the two conditions (increased blood viscosity), RBC sickling was not statistically affected by either exercise or hydration/dehydration conditions (90).

Intensity. To date, no studies have investigated how exercise intensity may alter RBC sickling and/or other hemorheological markers affecting vascular function, or whether lowering exercise intensity changes the incidence of ECAST or similar adverse events with SCT carriers. Of note is that SCT deaths from physical readiness tests (PRT) in the military were usually in persons of low to moderate fitness, and although they were attempting to complete a timed test, the absolute workloads were low relative to what might be expected for a PRT.

CURRENT SCT POLICIES

Public health perspectives. Universal newborn screening for SCD and SCT is currently performed in all 50 states in the United States and the District of Columbia as a public health imperative. The early detection and intervention in the child with SCD reduces mortality compared with children diagnosed later (92). Several national health-related organizations have established policy positions regarding SCT screening related to athletic participation. The U.S. Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders of Newborns and Children supports the right of individuals to be informed about their medical risks of inherited conditions, but it emphasizes that testing should 1) be voluntary, 2) take place in a setting that ensures privacy, 3) not be required for athletic participation, and 4) provide athletes with information about strategies to avoid excessive dehydration and undue physical exertion as part of routine medical care (48).

The Sickle Cell Disease Association of America cited the lack of scientific evidence that would support a significant correlation between SCT in athletes and unexplained ED in the development of their policy. Sickle Cell Disease Association of America is in favor of implementation of universal, safe training guidelines to reduce dehydration and heat- or exercise-related illness and recommends voluntary screening be linked to counseling, before and after testing, to protect the individual against stigmatization and/or genetic discrimination.

ASH, representing more than 14,000 physicians and researchers in SCD and other blood disorders, also opposes SCT testing or disclosure of status as a prerequisite for athletic participation. ASH believes such screening cannot be justified on the basis of current scientific evidence (38) but strongly supports the implementation of universal guidelines to reduce exertion-related injuries and deaths. ASH policy also soundly encourages additional biomedical and population-based research on SCT and its relationship to adverse health events.

The NCAA athlete with SCT. In 1975, the NCAA published its first medical opinion on athletes with SCT participating in intense exercise. They noted that SCT was not a barrier to achieving the highest levels of athletic performance, and most athletes with SCT would complete their careers without any complications. However, medical concerns were voiced, particularly related to high-intensity exertion at altitude and when athletes with SCT are not appropriately conditioned for demanding physical activities, which is risky for all athletes.

The NCAA has recently revised these guidelines for SCT and currently recommends that all athletic departments within its three federated divisions confirm SCT status in all student athletes either from their newborn screening or from diagnostic medical testing during their preparticipation medical examinations. Beginning in 2010 for Division I and 2012 for Division II, SCT status confirmation is required of all student athletes when they begin their initial seasons of eligibility and when trying out for teams. Any student athlete may opt out of the diagnostic verification by signing a written release. If SCT is confirmed, the affected student athlete is offered counseling on the implications, including health, athletics, and family planning. In addition to SCT guidelines, the NCAA has guidelines in their *Sports Medicine Handbook* on emergency care, heat illness prevention, and preseason preparation. The NCAA believes that knowing SCT status provides one more layer of protection and creates the best environment for student athlete safety through prevention, personal care, and medical intervention.

The warfighter with SCT. The issue of SCT testing within the military has a long history. In the 1970s, the DoD, with help from the National Academy of Sciences National Research Council, revised the guidelines for recruits with various types of sickle cell conditions. This culminated in a 1973 Ad Hoc Committee on S-hemoglobinopathies (11,25,95), which provided recommendations implemented by all military services. Previous restrictions on diving, high-altitude parachuting, and admittance into the Special Forces remained intact (11), but incoming recruits with SCT would now be accepted for military flight duties, except for assignment as pilots or copilots (11,95).

In 1981, the DoD mandated all three services to permit SCT carriers with HbS ≤41%, as determined by electrophoresis, to perform all previously restricted duties (95). This directive was abruptly ended in 1985 by a DoD policy change to discontinue all occupational restrictions on individuals with SCT. The new guidelines delineated that no individual with SCT would be required to undergo screening, other than that required by all applicants for each respective occupation (95). Policies concerning SCT were revisited several years later, after the death of three Air Force recruits (81). Reevaluation of SCT screening in 1996 led to a memorandum (28) from the Secretary of Defense stating that SCT testing was not required at Military Entrance Processing Stations for military accessions. Military medical history screening guidelines were considered sufficient for excluding individuals with SCD, and the monetary cost of screening outweighed the anticipated benefit. Although testing would continue for individuals under consideration for specific occupational duties, it would only be performed after entry into the military (28).

Currently, each service is permitted to have its own policy based upon unique operational needs. The U.S. Air Force, U.S. Navy, and U.S. Marines screen for SCT after accession, whereas the Army discontinued all screening procedures in 1991. Admittance to occupational specialties within the U.S. Army is restricted to male and female recruits with hematocrit concentrations ≥38% and 35%, respectively, if a complete hematologic evaluation results in a diagnosis of anemia due to SCT or β-thalassemia. Navy recruits with SCT are issued a red wrist band to demarcate light duty, until completion of electrophoresis testing. Recruits with HbS ≥45% are separated from military service, whereas those with HbS <45% are issued red dog tags and a red-orange belt to wear during strenuous physical activities. They are also counseled on risk of exertion-induced symptoms/episodes when at altitude and the importance of proper hydration practices. Recruits are not counseled on the risk of sudden death and/or unexplained ED. SCT-positive U.S. Air Force recruits are eligible to separate from their service commitment, but those with HbS >45% are mandated to leave.

SUMMIT RECOMMENDATIONS

Mitigating ECAST risk in the WA. Whereas well-controlled interventional trials on persons with SCT are lacking, reducing the risk and episodes of ECAST are essential. Most ECAST episodes in the military and sports communities take place during basic training or preseason athletic training, respectively. Accordingly, preventive efforts for these populations should be prioritized to these periods. The National Athletic Trainer's Association published guidance to address heat stress and exercise intensity for all athletes—with and without SCT (2,14). Strict adherence to heat acclimatization and appropriate progression in exercise intensity are critical factors in mitigating risk for all WA. In particular, repeated high-intensity, timed exercise bouts with limited recovery should be avoided during the first 1 to 2 wk of conditioning for WA.

In military recruits, ECAST is most commonly observed during 1- to 2-mile timed runs. Recruits at highest risk are those who have repeatedly had difficulty passing the PRT. Runs conducted immediately after field training exercises

during summer and fall months appear to be especially high risk if no or insufficient rest time is allowed between such events. When conducting PRTs, military leaders should ensure that recruits are well hydrated and sufficiently rested, preferably coming from a shaded or indoor cooled environment. In addition, a minimum of 48 h should elapse between strenuous field training and PRT.

Contemporary prevention strategies also consider the risk of cumulative heat strain from high levels of exertion and heat exposure, which may occur during the 72 h preceding a training event (96). Thermally challenging (hot and/or humid) exposures, with minimal opportunities for "heat dumping" (exposure to air conditioning, cool showers, rest in shaded areas, and removal of heavy protective equipment/uniform layers), alone or in combination with other contributing risk factors, such as prior/current illness, insufficient sleep, medications, dietary supplements, and lack of acclimation, and physical conditioning, can measurably exacerbate thermal strain and EHI risk in all WA.

Emergent management of WA with ECAST. No evidence-based guidelines for managing an ECAST event are currently available. However, contemporary best practice for WA with suspected ECAST should follow a "chain of survival" and prompt execution of an effective emergency action plan emphasizing rapid recognition and early interventions as outlined in Figure 1.

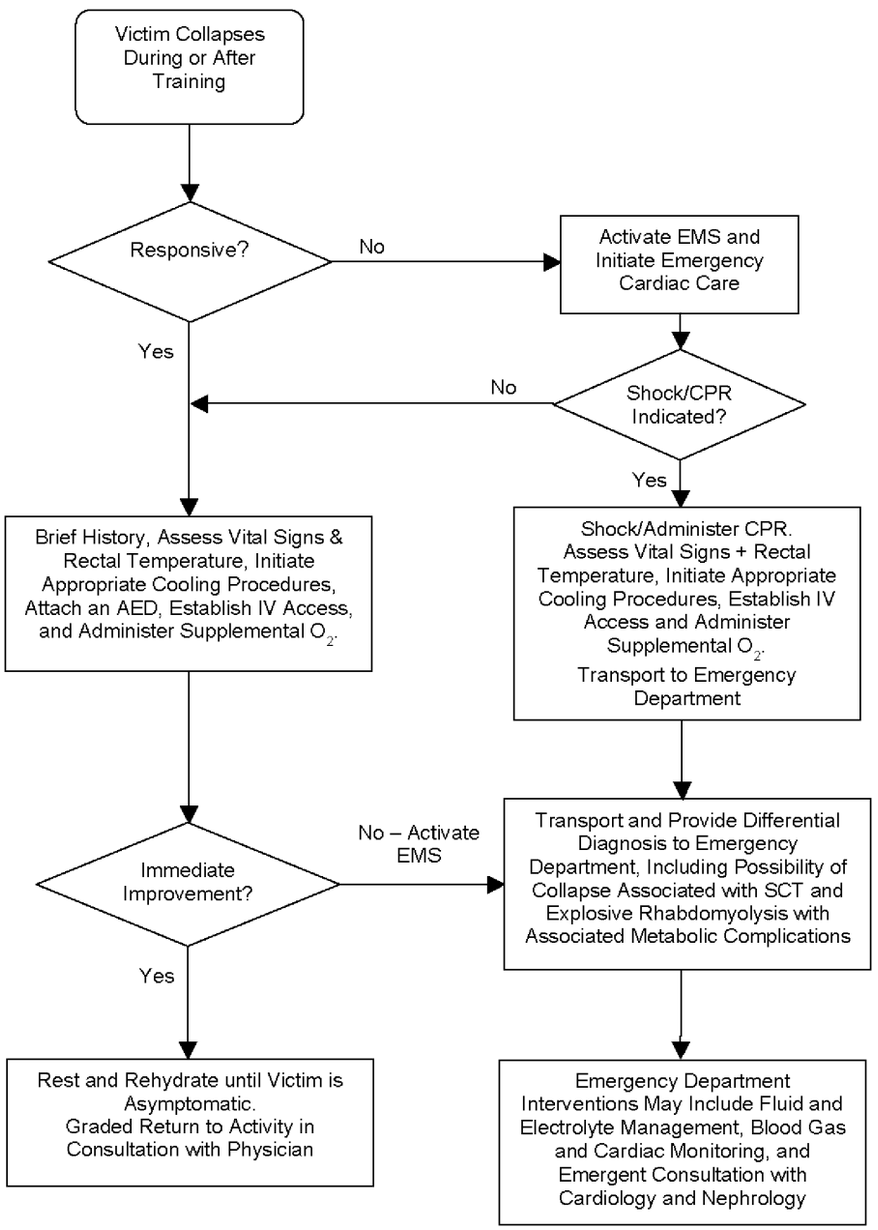

FIGURE 1—Recommendations for treating ECAST events in WA: chain of survival.

TABLE 3. ECAST RTDP guidelines.

- WA must be asymptomatic at rest and have normal end-organ function.
- Full medical history and physical examination before RDTP, with specific emphasis on identifying the presence of comorbidities, use of drugs and/or supplements, and both family and environmental risk factors.
- Graded RTDP under close supervision by medical personnel.
- Educate WA on the importance of proper hydration and possibility of subsequent ECAST events with high heat stress and exercise intensity.

RDTP, return to duty/return to play.

Critical to managing an ECAST event is communication with the receiving emergency department. The receiving facility must be made aware of the differential diagnosis and possibility of ECAST with accompanying explosive ER. Interventions in the emergency department include aggressive fluid and electrolyte management, blood gas monitoring to rule out metabolic acidosis, cardiac monitoring, and possibly dialysis to control hyperkalemia. Patients with severe ECAST may develop hyperkalemia and lethal cardiac arrhythmias within minutes to hours of syndrome onset (8,31). Any treatment to avert these outcomes should be instituted.

Return-to-play considerations in WA with ECAST. No evidence-based guidelines are available for RTDP after an episode of ECAST. Importantly, RTDP should only be considered once WAs are asymptomatic at rest and have normal end-organ function, as measured by conventional biomarkers (Table 3). Treating clinicians should obtain detailed histories and physicals on WA to identify comorbidities and other environmental/family-related risk factors. Graded RTDP programs/schedules with close supervision are recommended, despite limited supporting evidence. WA should be educated about physical activity and the risk of ECAST, with particular attention to hydration, heat, and exercise intensity. As noted earlier, physiological responses thought to increase the risk of ECAST can be lessened if WA remain hydrated (8,90); accordingly, the importance of hydration must be emphasized. Persons with SCT may require more fluid to remain in a euhydrated state than WA without SCT, based on a potential reduced ability to concentrate urine (26). Table 4 outlines current recommendations used at the University of Oklahoma to mitigate ECAST risk.

The WA with a history of ECAST should be made aware that altitude, illness, and dietary supplements are also potential contributing risk factors for ECAST. WA should be given sufficient time to acclimatize to altitude, modification of duty/activity should be considered when WA are or were recently ill, and all nutraceuticals/dietary supplements should be carefully reviewed, as many contain stimulants and sympathomimetics that can increase metabolic heat load (34). Continued activity and intensity beyond when an individual would normally stop or moderate should be discouraged (35). Importantly, similar precautions should be followed in WA without SCT.

Although most WA with a history of ECAST should be able to RTDP and operate effectively without restrictions, occasionally, an ECAST event may result in significant complications or recurrence. In these cases, genetic testing for potential associated abnormalities and consultation with a hematologist familiar with SCT and exercise are recommended.

RESEARCH PRIORITIES

Some knowledge gaps have been identified throughout this review. Accordingly, Table 5 presents an overview of types of research and respective study considerations. Given the low rate of fatal ECAST cases, an event should be declared sentinel and investigated to consider other factors discussed in this review. Public health surveillance of ECAST events will be critical in identifying potential cases; these could then be studied for similarities and possible causes. Unfortunately, rigorous clinical studies are lacking, expensive, and difficult to carry out. For example, designing a study to evaluate the risk of exercise intensity involves ethical risks as well, if intensity is indeed a primary contributing factor. Likewise, studies in the heat are potentially risky if SCT is indeed associated with heat intolerance and clinical risk. However, many questions and contributing factors can be addressed to determine the relative contribution of SCT to ECAST events. Combining retrospective and prospective epidemiological data from ECAST events with ongoing clinical research will most likely provide new information to bridge critical knowledge gaps.

CONCLUSION

The summit and expert panel established recommendations regarding exercise and SCT that can be implemented to

TABLE 4. Strategies for mitigating risk in WA.

- Encourage WA to participate in strength and conditioning programs consistent with their individual needs and abilities, before enlistment and/or beginning/returning to sport activity. Emphasize importance of year-round periodized conditioning.
- Use gradual training progressions and program longer periods of rest and recovery between repetitive sprints/drills, especially during preseason/basic training and after periods of extended rest and/or illness/injury.
- Focus initial basic training and preseason conditioning on the progressive establishment of an aerobic fitness base and environmental (heat or altitude) acclimatization.
- Avoid timed runs, repeated intervals, or preseason conditioning tests early in the training cycle and/or immediately after field/sport training exercises. A minimum of 48 h should elapse between field training and fitness testing.
- Decrease total volume of activity and adjust work/rest intervals during hot and/or humid conditions.
- Stop activity immediately with onset of symptoms (i.e., muscle pain and/or cramping, swelling, weakness, tenderness, breathlessness, and fatigue).
- Encourage WA to report any symptoms immediately to appropriate medical and/or leadership personnel.
- Provide and promote consumption of readily accessible fluids at regular intervals before, during, and after activity.
- Monitor WAs who are new to altitude; adjust activity accordingly.
- Prohibit/adjust activity if WAs are currently or were recently ill.
- Educate WA with SCT on conditions (i.e., heat stress, altitude, dehydration, illness, dietary supplements, medications) that increase their risk for ECAST.
- Ensure that personnel and facilities for treating heat illness are readily available on site and that a proper emergency action plan has been developed and rehearsed before the occurrence of an ECAST event.

TABLE 5. Research categories and considerations.

Epidemiological	Preventive Health	Clinical Research
Prospective studies on large cohorts of collegiate athletes and military basic training recruits to compile careful protocol-driven records, to include the following:	Assess the efficacy of current risk mitigation strategies (i.e., hydration, heat, and exercise intensity) used in collegiate athletics and/or the military.	Conduct DNA testing on all ED/EDU to clearly identify ethnicity, full screening of Hb genes, and other genetic abnormalities, initially focusing on the following:
• Prior medical histories and physical examination records.		• Cardiac channelopathies.
• Screening data for hematologic, genetic, cardiac, and metabolic risk factors.		• Ryanodine receptor variants, hemorheology abnormalities.
• Training or conditioning routines		• ICAM and VCAM blood viscosity.
• Weather data and climate trends		• RBC deformability
• Collateral information on any drug/dietary supplement use.	Assess risks and benefits of service-specific and NCAA's SCT screening programs, as they pertain to the following:	Conduct testing to quantify percentage HbS in blood samples from all ECAST events.
• Clinical events associated with ECAST, including both laboratory and clinical outcomes.	• Outcome (# ECAST events).	Conduct muscle biopsy and cardiac tissue sampling on all fatal ECAST events.
• When appropriate, postmortem examinations.	• Program cost-effectiveness.	Conduct studies to assess various alterations in training methods/routines to assess associated risks.
	• Potential discriminatory implications and effects.	Conduct clinical trials of interventions to reduce/eliminate risks.

ED, exercise-related death; EDU, exertional deaths unexplained; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule.

improve the health of all—not just those with SCT. Further research is needed before conclusions can be drawn regarding the etiology of the increased death rate observed in WA with SCT, and the possibility exists that SCT is a surrogate for as yet another contributing factor for the unexplained deaths.

The authors acknowledge that the DoD-ACSM workshop involved more than 30 professionals including not only speakers and the writing group but also experts and other guests from both the military and civilian sports medicine and training communities.

The authors thank conference coordinators Jane Senior, ACSM Assistant Executive Vice President, Research Administration and Programs, and Stacey Zeno, Program Manager, CHAMP, USU.

The authors acknowledge that this DoD-ACSM summit was made possible by educational support from the Uniformed Services University CHAMP, the US Army Training and Doctrine Command, the Defense Health Program, the AMSSM, the ACSM, and the NCAA. The authors report no conflict of interest.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Army, the DoD, Uniformed Services University, the NCAA, or the ACSM.

REFERENCES

1. Adachi K, Asakura T. Polymerization of AS hybrid hemoglobin. Potent inhibitory effect of hemoglobin A on the polymerization of AS hybrid hemoglobin. *J Biol Chem*. 1984;259(4):2108–12.
2. Anderson S, Eichner RE. National Athletic Trainers' Association Consensus Statement: sickle cell trait and the athlete. Anaheim, CA2007; [Accessed May 23 2012]. Available from: http://www.nata.org/sites/default/files/SickleCellTraitAndTheAthlete.pdf.
3. Anzalone ML, Green VS, Buja M, Sanchez LA, Harrykissoon RI, Eichner ER. Sickle cell trait and fatal rhabdomyolysis in football training: a case study. *Med Sci Sports Exerc*. 2010;42(1):3–7.
4. Aufradet E, Monchanin G, Oyonno-Engelle S, et al. Habitual physical activity and endothelial activation in sickle cell trait carriers. *Med Sci Sports Exerc*. 2010;42(11):1987–94.
5. Ballas SK, Mohandas N. Sickle red cell microrheology and sickle blood rheology. *Microcirculation*. 2004;11(2):209–25.
6. Ballas SK, Smith ED. Red blood cell changes during the evolution of the sickle cell painful crisis. *Blood*. 1992;79(8):2154–63.
7. Beltan E, Chalabi T, Tripette J, Chout R, Connes P. Coagulation responses after a submaximal exercise in sickle cell trait carriers. *Thromb Res*. 2011;127(2):167–9.
8. Bergeron MF, Cannon JG, Hall EL, Kutlar A. Erythrocyte sickling during exercise and thermal stress. *Clin J Sport Med*. 2004;14(6):354–6.
9. Bile A, Le Gallais D, Mercier B, Martinez P, Ahmaidi S, Prefaut C. Anaerobic exercise components during the force-velocity test in sickle cell trait. *Int J Sports Med*. 1996;17(4):254–8.
10. Bile A, Le Gallais D, Mercier J, Bogui P, Prefaut C. Sickle cell trait in Ivory Coast athletic throw and jump champions, 1956–1995. *Int J Sports Med*. 1998;19(3):215–9.
11. Brodine CE, Uddin DE. Medical aspects of sickle hemoglobin in military personnel. *J Natl Med Assoc*. 1977;69(1):29–32.
12. Burke J, Seda G, Allen D, Knee TS. A case of severe exercise-induced rhabdomyolysis associated with a weight-loss dietary supplement. *Mil Med*. 2007;172(6):656–8.
13. Capacchione JF, Sambuughin N, Bina S, Mulligan LP, Lawson TD, Muldoon SM. Exertional rhabdomyolysis and malignant hyperthermia in a patient with ryanodine receptor type 1 gene, L-type calcium channel alpha-1 subunit gene, and calsequestrin-1 gene polymorphisms. *Anesthesiology*. 2010;112(1):239–44.
14. Casa DJ, Csillan D, Armstrong LE, et al. Preseason heat-acclimatization guidelines for secondary school athletics. *J Athl Train*. 2009;44(3):332–3.
15. Chirico EN, Martin C, Faes C, et al. Exercise training blunts oxidative stress in sickle cell trait carriers. *J Appl Physiol*. 2012;112(9):1445–53.
16. Connes P. Hemorheology and exercise: effects of warm environments and potential consequences for sickle cell trait carriers. *Scand J Med Sci Sports*. 2010;20(3 suppl):S48–52.
17. Connes P, Frank S, Martin C, et al. New fundamental and applied mechanisms in exercise hemorheology. *Clin Hemorheol Microcirc*. 2010;45(2–4):131–41.

18. Connes P, Harmon KG, Bergeron MF. Pathophysiology of exertional death associated with sickle cell trait: can we make a parallel with vaso-occlusion mechanisms in sickle cell disease? *Br J Sports Med.* [Internet]. 2012 [cited 2012 May 22];2012 May 19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22611148. doi:10.1136/bjsports-2012-091223.
19. Connes P, Hue O, Hardy-Dessources MD, Boucher JH, Pichot V, Barthelemy JC. Hemorheology and heart rate variability: is there a relationship? *Clin Hemorheol Microcirc*. 2008;38(4):257–65.
20. Connes P, Hue O, Tripette J, Hardy-Dessources MD. Blood rheology abnormalities and vascular cell adhesion mechanisms in sickle cell trait carriers during exercise. *Clin Hemorheol Microcirc*. 2008;39(1–4):179–84.
21. Connes P, Perrey S, Sara F, Hardy-Dessources MD, Hedreville M, Hue O. Lactate removal ability and VO2 recovery kinetics in sickle cell trait carriers compared with normal haemoglobin subjects: preliminary data. *TOSMJ*. 2009;3:49–54.
22. Connes P, Racinais S, Sra F, et al. Does the pattern of repeated sprint ability differ between sickle cell trait carriers and healthy subjects. *Int J Sports Med*. 2006;27(12):937–42.
23. Connes P, Reid H, Hardy-Dessources MD, Morrison E, Hue O. Physiological responses of sickle cell trait carriers during exercise. *Sports Med*. 2008;38(11):931–46.
24. Connes P, Tripette J, Chalabi T, et al. Effects of strenuous exercise on blood coagulation activity in sickle cell trait carriers. *Clin Hemorheol Microcirc*. 2008;38(1):13–21.
25. Diggs LW. The sickle cell trait in relation to the training and assignment of duties in the Armed Forces: I. Policies, observations, and studies. *Aviat Space Environ Med*. 1984;55(3):180–5.
26. Diggs LW. The sickle cell trait in relation to the training and assignment of duties in the armed forces: III. Hyposthenuria, hematuria, sudden death, rhabdomyolysis, and acute tubular necrosis. *Aviat Space Environ Med*. 1984;55(5):358–64.
27. Dillard TA, Kark JA, Rajagopal KR, Key JA, Canik JJ, Ruehle CJ. Pulmonary function in sickle cell trait. *Ann Intern Med*. 1987;106(2):191–6.
28. Dorn E. Memorandum on Sickle Cell Policy: Modification of Department of Defense Instruction 6465.1. Washington, DC 1996; [Accessed May 23 2012]. Available from: http://www.tricare.mil/policy/fy97/sckl9718.html.
29. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. *Ann Intern Med*. 2004;141(11):829–34.
30. Eichner ER. Sickle cell trait. *J Sport Rehabil*. 2007;16(3):197–203.
31. Eichner ER. Sports medicine pearls and pitfalls–sickle cell trait and athletes: three clinical concerns. *Curr Sports Med Rep*. 2007;6(3):134–5.
32. Eichner ER. Overcaffeination: low potassium and other perils. *Curr Sports Med Rep*. 2011;10(3):122–3.
33. Eichner ER. Sickle cell considerations in athletes. *Clin Sports Med*. 2011;30(3):537–49.
34. Ely BR, Ely MR, Cheuvront SN. Marginal effects of a large caffeine dose on heat balance during exercise-heat stress. *Int J Sport Nutr Exerc Metab*. 2011;21(1):65–70.
35. Figueredo VM. Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart. *Am J Med*. 2011;124(6):480–8.
36. Gardner JW, Gutmann FD, Potter RN, Kark JA. Nontraumatic exercise-related deaths in the U.S. military, 1996–1999. *Mil Med*. 2002;167(12):964–70.
37. Gladwin MT, Schechter AN, Ognibene FP, et al. Divergent nitric oxide bioavailability in men and women with sickle cell disease. *Circulation*. 2003;107(2):271–8.
38. Goldsmith JC, Bonham VL, Joiner CH, Kato GJ, Noonan AS, Steinberg MH. Framing the research agenda for sickle cell trait: building on the current understanding of clinical events and their potential implications. *Am J Hematol*. 2012;87(3):340–6.
39. Gozal D, Thiriet P, Mbala E, et al. Effect of different modalities of exercise and recovery on exercise performance in subjects with sickle cell trait. *Med Sci Sports Exerc*. 1992;24(12):1325–31.
40. Harmon KG, Drezner JA, Klossner D, Asif IM. Sickle cell trait associated with a RR of death of 37 times in National Collegiate Athletic Association football athletes: a database with 2 million athlete-years as the denominator. *Br J Sports Med*. 2012;46(5):325–30.
41. Harrelson GL, Fincher AL, Robinson JB. Acute exertional rhabdomyolysis and its relationship to sickle cell trait. *J Athl Train*. 1995;30(4):309–12.
42. Hebbel RP, Yamada O, Moldow CF, Jacob HS, White JG, Eaton JW. Abnormal adherence of sickle erythrocytes to cultured vascular endothelium: possible mechanism for microvascular occlusion in sickle cell disease. *J Clin Invest*. 1980;65:154–60.
43. Hedreville M, Connes P, Romana M, et al. Central retinal vein occlusion in a sickle cell trait carrier after a cycling race. *Med Sci Sports Exerc*. 2009;41(1):14–8.
44. Henderson AB, Gray HO. Studies of sickle cell disease. II. Hematuria in a case of sickle cell disease. *J Natl Med Assoc*. 1959;51(2):97–101.
45. Hicksg EJ, Griep JA, Nordschow CD. Comparison of results for three method of hemoglobin S identification. *Clin Chem*. 1973;19(5):533–5.
46. Hue O, Julan ME, Blonc S, et al. Alactic anaerobic performance in subjects with sickle cell trait and hemoglobin AA. *Int J Sports Med*. 2002;23(3):174–7.
47. Jones SR, Binder RA, Donowho EM Jr. Sudden death in sickle cell trait. *N Engl J Med*. 1970;282(6):323–5.
48. Jordan LB, Smith-Whitley K, Treadwell MJ, Telfair J, Grant AM, Ohene-Frempong K. Screening U.S. college athletes for their sickle cell disease carrier status. *Am J Prev Med*. 2011;41(6):S406–12.
49. Kark JA, Labotka RJ, Gardner JW, Ward FT. Prevention of exercise-related death unexplained by preexisting disease (EDU) associated with sickle cell trait (SCT) without hemoglobin (Hb) screening or Hb specific management. *Blood*. 2010;116(21):416–7.
50. Kark JA, Posey DM, Schumacher HR, Ruehle CJ. sickle cell trait as a risk factor for sudden death in physical training. *N Engl J Med*. 1987;317(13):781–7.
51. Kark JA, Ward FT. Exercise and hemoglobin S. *Semin Hematol*. 1994;31(3):181–225.
52. Key NS, Derebail VK. sickle cell trait: novel clinical significance. *Hematology Am Soc Hematol Educ Program*. 2010;1:418–22.
53. Key NS, Slungaard A, Dandelet L, et al. Whole blood tissue factor procoagulant activity is elevated in patients with sickle cell disease. *Blood*. 1998;91(11):4216–23.
54. Le Gallais D, Lonsdorfer J, Bogui P, Fattoum S. Point: Sickle cell trait should be considered asymptomatic and as a benign condition during physical activity. *J Appl Physiol*. 2007;103(6):2137–8; discussion 41.
55. Le Gallais D, Prefaut C, Dulat C, Macabies J, Lonsdorfer J. Sickle cell trait in Ivory Coast athletic champions, 1956–1989. *Int J Sports Med*. 1991;12(5):509–10.
56. Le Gallais D, Prefaut C, Mercier J, Bile A, Bogui P, Lonsdorfer J. Sickle cell trait as a limiting factor for high-level performance in a semi-marathon. *Int J Sports Med*. 1994;15(7):399–402.
57. Loosemore M, Walsh SB, Morris E, Stewart G, Porter JB, Montgomery H. Sudden exertional death in sickle cell trait. *Br J Sports Med*. 2012;46(5):312–4.
58. Malekgoudarzi B, Feffer S. Myonecrosis in sickle cell anemia. *N Engl J Med*. 1999;340(6):483.
59. Manci EA, Maisel DA, Conrad ME. Systemic necrotizing vasculitis in sickle cell disease. *Am J Hematol*. 1987;26(1):93–6.

60. Marlin L, Connes P, Antoine-Jonville S, et al. Cardiorespiratory responses during three repeated incremental exercise tests in sickle cell trait carriers. *Eur J Appl Physiol*. 2008;102(2):181–7.
61. Marlin L, Etienne-Julan M, Le Gallais D, Hue O. Sickle cell trait in French West Indian elite sprint athletes. *Int J Sports Med*. 2005;26(8):622–5.
62. Marlin L, Sara F, Antoine-Jonville S, Connes P, Etienne-Julan M, Hue O. Ventilatory and lactic thresholds in subjects with sickle cell trait. *Int J Sports Med*. 2007;28(11):916–20.
63. Martin TW, Weisman IM, Zeballos RJ, Stephenson SR. Exercise and hypoxia increase sickling in venous blood from an exercising limb in individuals with sickle cell trait. *Am J Med*. 1989; 87(1):48–56.
64. Messonnier L, Samb A,]Tripette J, et al. Moderate endurance exercise is not a risk for rhabdomyolysis or renal failure in sickle cell trait carriers. *Clin Hemorheol Microcirc*. 2012;51(3):193–202.
65. Mitchell BL. Sickle cell trait and sudden death—bringing it home. *J Natl Med Assoc*. 2007;99(3):300–5.
66. Monchanin G, Connes P, Wouassi D, et al. Hemorheology, sickle cell trait, and alpha-thalassemia in athletes: effects of exercise. *Med Sci Sports Exerc*. 2005;37(7):1086–92.
67. Monchanin G, Serpero LD, Connes P, et al. Plasma levels of adhesion molecules ICAM-1 and VCAM-1 in athletes with sickle cell trait with or without alpha-thalassemia during endurance exercise and recovery. *Clin Hemorheol Microcirc*. 2008;40(2): 89–97.
68. Monchanin G, Serpero LD, Connes P, et al. Effects of a progressive and maximal exercise on plasma levels of adhesion molecules in athletes with sickle cell trait with or without {alpha}-thalassemia. *J Appl Physiol*. 2007;102(1):169–73.
69. Morrison EY, Cooper PD. Some bio-medical mechanisms in athletic prowess. *West Indian Med J*. 2006;55(3):205–9.
70. Nebor D, Bowers A, Hardy-Dessources MD, et al. Frequency of pain crises in sickle cell anemia and its relationship with the sympatho-vagal balance, blood viscosity and inflammation. *Haematologica*. 2011;96(11):1589–94.
71. Okpala I. Leukocyte adhesion and the pathophysiology of sickle cell disease. *Curr Opin Hematol*. 2006;13(1):40–4.
72. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med*. 1991;325(1):11–6.
73. Presley TD, Perlegas AS, Bain LE, et al. Effects of a single sickling event on the mechanical fragility of sickle cell trait erythrocytes. *Hemoglobin*. 2010;34(1):24–36.
74. Ramirez A, Hartley LH, Rhodes D, Abelmann WH. Morphological features of red blood cells in subjects with sickle cell trait: changes during exercise. *Arch Intern Med*. 1976;136(9):1064–6.
75. Robinson JR, Stone WJ, Asendorf AC. Exercise capacity of black sickle cell trait males. *Med Sci Sports*. 1976;8(4):244–5.
76. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. *Orphanet J Rare Dis*. 2007;2:21.
77. Sara F, Connes P, Hue O, Montout-Hedreville M, Etienne-Julan M, Hardy-Dessources MD. Faster lactate transport across red blood cell membrane in sickle cell trait carriers. *J Appl Physiol*. 2006;100(2):437–42.
78. Scheinin L, Wetli CV. Sudden death and sickle cell trait: medicolegal considerations and implications. *Am J Forensic Med Pathol*. 2009;30(2):204–8.
79. Scoville SL, Gardner JW, Magill AJ, Potter RN, Kark JA. Nontraumatic deaths during U.S. Armed Forces basic training, 1977–2001. *Am J Prev Med*. 2004;26(3):205–12.
80. Sheikha A. Splenic syndrome in patients at high altitude with unrecognized sickle cell trait: splenectomy is often unnecessary. *Can J Surg*. 2005;48(5):377–81.
81. Sherry P. Sickle cell trait and rhabdomyolysis: case report and review of the literature. *Mil Med*. 1990;155(2):59–61.
82. Smith LE, Kark JA, Gardner JW, Ward FT. Unrecognized exertional heat illness as a risk factor for exercise-related sudden cardiac death among young adults. *J Am Coll Card*. 1997;29(suppl A): 447–8A.
83. Tageja N, Racovan M, Valent J, Zonder J. Myonecrosis in sickle cell anemia-overlooked and underdiagnosed. *Case Report Med*. 2010;2010:659031.
84. Thiriet P, Le Hesran JY, Wouassi D, Bitanga E, Gozal D, Louis FJ. Sickle cell trait performance in a prolonged race at high altitude. *Med Sci Sports Exerc*. 1994;26(7):914–8.
85. Thogmartin JR, Wilson CI, Palma NA, Ignacio SS, Shuman MJ, Flannagan LM. Sickle cell trait-associated deaths: a case series with a review of the literature. *J Forensic Sci*. 2011;56(5):1352–60.
86. Tripette J, Alexy T, Hardy-Dessources MD, et al. Red blood cell aggregation, aggregate strength and oxygen transport potential of blood are abnormal in both homozygous sickle cell anemia and sickle-hemoglobin C disease. *Haematologica*. 2009;94(8): 1060–5.
87. Tripette J, Connes P, Beltan E, et al. Red blood cell deformability and aggregation, cell adhesion molecules, oxidative stress and nitric oxide markers after a short term, submaximal, exercise in sickle cell trait carriers. *Clin Hemorheol Microcirc*. 2010;45 (1):39–52.
88. Tripette J, Connes P, Hedreville M, et al. Patterns of exercise-related inflammatory response in sickle cell trait carriers. *Br J Sports Med*. 2010;44(4):232–7.
89. Tripette J, Hardy-Dessources MD, Sara F, et al. Does repeated and heavy exercise impair blood rheology in carriers of sickle cell trait? *Clin J Sport Med*. 2007;17(6):465–70.
90. Tripette J, Loko G, Samb A, et al. Effects of hydration and dehydration on blood rheology in sickle cell trait carriers during exercise. *Am J Physiol Heart Circ Physiol*. 2010;299(3):H908–14.
91. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. *Am J Med*. 2009;122(6):507–12.
92. Vichinsky E, Hurst D, Earles A, Kleman K, Lubin B. Newborn screening for sickle cell disease: effect on mortality. *Pediatrics*. 1988;81(6):749–55.
93. Vincent L, Feasson L, Oyono-Enguelle S, et al. Remodeling of skeletal muscle microvasculature in sickle cell trait and alpha-thalassemia. *Am J Physiol Heart Circ Physiol*. 2010;298(2): H375–84.
94. Vincent L, Feasson L, Oyono-Enguelle S, et al. Skeletal muscle structural and energetic characteristics in subjects with sickle cell trait, alpha-thalassemia, or dual hemoglobinopathy. *J Appl Physiol*. 2010;109(3):728–34.
95. Voge VM, Rosado NR, Contiguglia JJ. Sickle cell anemia trait in the military aircrew population: a report from the Military Aviation Safety Subcommittee of the Aviation Safety Committee, AsMA. *Aviat Space Environ Med*. 1991;62(11):1099–102.
96. Wallace RF, Kriebel D, Punnett L, et al. The effects of continuous hot weather training on risk of exertional heat illness. *Med Sci Sports Exerc*. 2005;37(1):84–90.
97. Weisman IM, Zeballos RJ, Johnson BD. Cardiopulmonary and gas exchange responses to acute strenuous exercise at 1,270 meters in sickle cell trait. *Am J Med*. 1988;84(3 Pt 1):377–83.
98. Weisman IM, Zeballos RJ, Johnson BD. Effect of moderate inspiratory hypoxia on exercise performance in sickle cell trait. *Am J Med*. 1988;84(6):1033–40.
99. Weisman IM, Zeballos RJ, Martin TW, Johnson BD. Effect of Army basic training in sickle cell trait. *Arch Intern Med*. 1988; 148(5):1140–4.
100. Westerman MP, Green D, Gilman-Sachs A, et al. Coagulation changes in individuals with sickle cell trait. *Am J Hematol*. 2002; 69(2):89–94.