Exercise Collapse Associated with Sickle Cell Trait (ECAST): Case Report and Literature Review

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Abstract
Sickle cell trait (SCT) has been associated with exertional collapse (ECAST) and exercise-related sudden death in athletes and military warfighters. The mechanisms underlying ECAST remain controversial in the sports medicine community. Multiple case presentations and anecdotal reports postulate the role of extraordinary exercise intensity, but other risk factors including dehydration, heat, previous exertional rhabdomyolysis, genetic cofactors, and dietary supplements have been cited as potential contributors. Others have hypothesized some of the aforementioned factors combining in a “perfect storm” to trigger ECAST with a resultant potentially fatal “metabolic crisis.” This case report provides a brief review of SCT as it pertains to exercise in warfighters and athletes, identifies known and postulated risk factors associated with ECAST, and introduces the potential mechanistic role of the “double hit” as a contributor to ECAST.

A Tragic Case of Exercise Collapse Associated with Sickle Cell Trait (ECAST)
A 20-year-old otherwise healthy African-American male college student was unable to complete his fitness assessment due to severe leg pain and weakness 70 yd short of completing a 1.5-mile run. The patient had performed push-ups and sit-ups without difficulty immediately before the run. He was assisted off course, given water, and allowed to rest. When his symptoms did not improve, he was transported to the medical clinic. His only complaint was ongoing severe thigh and hamstring pain that made it difficult to walk. He denied use of medications, nutritional or ergogenic agents, or recent illness.

He previously had completed numerous vigorous, required military training evolutions with no apparent problems. The patient trained regularly for his semiannual physical fitness assessment tests, which required running 1.5 miles in less than 10 min and 30 s in addition to maximum push-ups and sit-ups performed in 1 min. He played intramural soccer on a nearly daily basis. Even though he had failed multiple prior brigade-wide fitness runs, he passed each run on makeup testing. Over the prior 2 years, he had complained of exertional “muscle cramps” in his legs with increasingly longer recovery times.

Notable on examination at the time of collapse was extreme tenderness to palpation in bilateral quadriceps and hamstrings, with pain on full extension of the knee or with flexion beyond 80°. Initial laboratory results included creatine kinase (CK) 5,662 IU·L⁻¹, lactate dehydrogenase (LDH) 1,332 IU·L⁻¹, and a trace of “blood” on urinalysis dipstick testing, with no red cells on urine microanalysis. He was diagnosed with exertional rhabdomyolysis (ER) and improved symptomatically after intravenous saline hydration. He was released with written instructions to increase oral hydration and avoid exertion until cleared medically. Two days later, by telephone, he reported progressive resolution of symptoms.

At 1-wk follow-up, his symptoms nearly had resolved except for quadriceps pain during deep squats and running, which had been performed prior to medical clearance. CK decreased to 1,351 IU·L⁻¹, with slight residual elevations of LDH, aspartate aminotransferase, and alanine aminotransferase. He was ordered to restrict strenuous activity for another week.

Despite repeated personal notifications, the patient failed to return to clinic until 3 wk later, when he again collapsed 20 yd short of the finish during a makeup fitness run, complaining of acute, severe leg cramps. The ambient temperature during the fitness run was again cool, and the patient claimed to have hydrated well even though he did note...
increased thirst, urination, and weight loss over the preceding week. The examination result was again remarkable only for quadriceps spasm, with marked tenderness to palpation and pain on passive stretch, with no recorded changes in mental status. Laboratory results prior to intravenous intervention included blood glucose 389 mg·dL⁻¹, bicarbonate 16 mEq·L⁻¹, potassium 3.3 mEq·L⁻¹, and CK 918 IU·L⁻¹. The working diagnosis given was dehydration and possible new-onset diabetic mellitus with ketoacidosis. He was given intravenous fluids and transferred to an intensive care unit.

Within hours, his legs became tense, mottled, and weak, with decreased sensation to light touch. His hyperglycemia normalized, but he quickly became acidic with hyperkalemia, hyperphosphatemia, and hypocalcemia. His urine turned brown with high myoglobin content. He received aggressive intravenous hydration, bicarbonate, furosemide for diuresis, and insulin for hyperkalemia. His urine output lagged well behind fluid input. By hospital day 2, a picture of disseminated intravascular coagulation (DIC) emerged, requiring transfusion with blood and plasma products. As the patient became more obtunded, compartment pressure testing revealed multiple compartment readings in the low 20s to mid-30s (mm Hg). He underwent multicompartiment fasciotomies of the thighs and lower legs. Acidosis and hyperkalemia remained problematic despite renal dialysis. He was kept sedated on ventilator following surgery. Subsequent serial examinations revealed gluteal compartment syndrome. He was taken back to the operating room for gluteal fasciotomies and further debridement of necrotic lower extremity muscles.

Despite improved management of acidosis and hyperkalemia, the DIC worsened and renal failure emerged. He underwent multiple debrideaments of the necrotic muscle, and amputation was considered. With a CK peak of 9 million IU·L⁻¹, hyperbaric oxygen therapy was begun to try to salvage nonnecrotic muscle. On hospital day 23, following a period of apparent clinical stabilization and improvement, no brainstem reflexes could be elicited. Computerized tomography and magnetic resonance imaging scans revealed infarcts throughout the upper cervical cord, brainstem, midbrain, and subcortical areas. After 3 d of absent higher neurologic function and following discussion with family, life support was withdrawn and the patient was pronounced dead.

Autopsy confirmed multiple infarcts throughout the brain, spleen, and kidneys, consistent with sickling. Postmortem tests were positive for SCT.

Introduction

In SCT, the mutation that encodes for an abnormal “sickle” beta hemoglobin chain is inherited from one parent and combines with one normal beta chain from the other parent, leading to the production of both sickle hemoglobin (HbS) and normal adult HbA tetramers within each red blood cell (34). SCT is more common in malarial regions of the world where it helps prevent early malarial death (7,17). SCT is one of the most common hemoglobin disorders, affecting more than 100 million people worldwide (20). In the United States, SCT is found in 8% of African-Americans, 0.5% of Hispanics, and 0.2% of Caucasians (4).

SCT traditionally is believed to be benign, with complications that are rare and mild (28). More recently, however, SCT has been associated with both ER and exercise-related death (ERD) in athletes and members of the military. In 2010, the National Collegiate Athletic Association (NCAA) enacted new policy and guidance on SCT requiring all student-athletes to provide documentation of their SCT status or sign a written release before beginning athletic activity (22). Although enacted in response to student-athlete complications and deaths associated with SCT, the basis for screening and the complex ethical ramifications for those identified as SCT positive have been hotly debated (34). The American Society of Hematology made policy reversal recommendations to the NCAA in 2012 based on ethical grounds and the lack of scientific evidence to support NCAA policy (20). Military screening practices and management of those identified with SCT are variable and based on the individual branch of service.

Epidemiology

The absolute number of athletes and military members who die from ECAST is relatively low (16,22). However, data collected on a cohort of 2.1 million Armed Forces recruits between 1977 and 1981 revealed increased relative risk of sudden unexplained exertional death, with SCT recruits 28 times more likely to die than other Black recruits and 40 times more likely to die than non-SCT recruits of all races. This equates to an absolute risk of 31 sudden unexplained deaths associated with SCT per 100,000 Black recruits (26). Harmon et al. (21) reviewed the cause of all cases of sudden death in NCAA student-athletes from January 2004 through December 2008 and found that the risk of exertional death in division I football players with SCT was 1:827, which was 37 times higher than that in athletes without SCT. Whereas studies in both civilian and military populations confirm the low absolute risk of exertional sudden death in those with SCT, they also validate an increased relative risk compared with those without SCT.

Pathophysiology

The mechanisms of collapse and ERD in athletes and warfighters with SCT remain controversial. One postulated mechanism of ECAST involves exertional sickling due to four major factors: profound lactic acidosis, extreme hyperoxemia in the circulation of working muscles, hyperthermia of working muscles, and dehydration of red cells coursing through those muscles (Fig. 1). While this hypothesis remains unproven, some believe that these four factors in concert precipitate sickling in the microcirculation of working muscles (1,16,34). A corollary hypothesis postulates that an exertional surge in epinephrine also may make sickle-trait red cells “sticky.” In theory, the resultant logjam of “sticky and stiff” sickle cells (31) in the microcirculation cuts blood supply to working muscles (12,32,33) and could lead to a fatal “metabolic storm” from explosive rhabdomyolysis (15,24).

While a causal relationship between exertional sickling and exercise-associated death is physiologically plausible, it is challenging to prove. Widespread, multiorgan, small-vessel sickling is seen commonly at autopsy, and it is difficult to determine whether this sickling was the proximate
cause of death or a secondary consequence of agonal metabolic changes (3,27,30).

**Potential Risk Factors**

Perhaps most perplexing is that fatal ECAST is not more common. Indeed it seems that most SCT athletes recognize or report no symptoms from their condition and train and compete without consequence. Some Olympic medalists in endurance events have SCT and report no lifetime incidence of ECAST symptoms. ECAST does not occur the first time the athlete exercises and even may not occur the first time he or she exercises in the heat or at altitude, even though this has occurred in some. So a fundamental question in ECAST is: why did this athlete with SCT die on this day?

While the real answer is “we do not know,” current thinking is that for that athlete on that day, a “confluence of cofactors” may cause an ECAST event. The workout was perhaps too intense or lasted too long, or maybe the cumulative heat exposure was too great, etc. — and that sustained maximal exertion in the face of SCT evoked grave exertional sickling and so ECAST. As experience with ECAST accumulates, ECAST increasingly is viewed as multifactorial, with possible environmental, metabolic, genetic, hematologic, and/or medical mechanisms combining for a “perfect storm” on that particular day. While recognizing that some factors may be more powerful than others and that many factors may span different categories, we describe as follows some conceptual categories and types of “sudden or unexpected perfect storms” that may trigger an ECAST event.

In the case presented in this article, a recent bout of ER may have lowered the midshipman’s threshold for a subsequent ECAST. Certainly metabolic abnormalities possibly favorable to ECAST have been shown to exist in the weeks and months after bouts of ER. A previous exposure to excessive heat, or unresolved exertional heat injury (EHI), also may play a role in a subsequent ECAST. While the precise risk for secondary EHI remains unclear, expert opinion is that an increased risk of EHI is likely for at least 3 to 6 months and may exist for years following EHI (25).

Two recent cases suggest a convergence of situational factors in ECAST (19). Two Army recruits, both in their ninth week of basic combat training, had failed the timed 2-mile Army Physical Fitness Test run several times. After a few days of rigorous field exercises, with limited sleep, and under moderate ambient conditions of temperature and humidity, both were urged on by their drill sergeants to meet the minimal run times. Both collapsed with leg pain and soon died from complications attributed by medical examiners to exertional sickling. In each of these cases, the sickling trigger appeared to be intense, sustained exertion, not EHI. These two cases and the introductory case reported here suggest that serial attempts to run a given distance in a given time, compounded perhaps by a preceding EK event or musculoskeletal stressor, may “stack” subclinical sickling situational events that may lower the threshold for fatal ECAST.

Research has demonstrated that the ability of SCT carriers to perform repeated short bouts of aerobic-predominant exercise, with limited recovery between bouts, may be lower than that of non-SCT carriers (10). Even though preliminary data (13) do not support compromised aerobic recovery in SCT carriers (11), further study is warranted (34). Some data (40) suggest lower cytochrome C oxidase activity in muscle.

![Figure 1](https://example.com/figure1.png)

**Figure 1:** A proposed schematic of the pathophysiological processes, which might culminate in exertional death in subjects with SCT: a final common pathway of hyperkalemia is suggested (30). (Reprinted from Loosemore M, Walsh SB, Morris E, et al. Sudden exertional death in sickle cell trait. *Br. J. Sports Med.* 2011;46:312–314. Copyright © 2011 BMJ Publishing Group Ltd. Used with permission.)
in SCT carriers, which could limit oxidative energy metabolism and lower aerobic capacity (34). A theoretic “metabolic double hit” may involve repeat episodes of lactic acidosis that may create a tipping point for resultant sickling and ECAST.

In theory, factors that increase the risk for EHI and ER may help create the perfect lactic acidosis storm for an ECAST “metabolic double hit.” One example (34) is the gene variant in the ryosyn induced type 1 receptor, which may evoke a hypermetabolic response and predispose individuals to EHI, ER, and malignant hyperthermia (9,36).

 Carnitine palmitoyltransferase 2 (CPT-2) deficiency or other metabolic myopathies theoretically could contribute also to a “metabolic double hit” scenario. CPT-2 is required to oxidize fatty acids. Most patients with the myopathic form of CPT-2 deficiency present as adolescents or young adults and have at least one copy of a mutation allowing some residual fatty acid oxidation in fibroblasts (5). When oxidation of fatty acids is defective, however, fats released from adipose tissue with fasting can accumulate in the liver, muscle, and heart. These fats can impair muscle function and lead to metabolic myopathy. Muscle fibers then can break down during sustained strenuous exercise, cold, fever, or prolonged fasting, causing muscle pain and elevation of CK (29) and lactic acidosis.

In addition to the aforementioned metabolic myopathic gene defects, variation in the sickle gene may contribute in some way to the variation in ECAST events. The sickle gene has four main haplotypes, representing four different geographic mutation origins: the Asian (Arab Indian) haplotype originating in central India or Saudi Arabia, the Benin haplotype originating in central West Africa, the Senegal haplotype originating in West Africa above the Niger River, and the Bantu (or CAR) haplotype originating in central West Africa above the Niger River, and the Bantu (or CAR) haplotype originating in central and south central Africa. The severity of sickle cell anemia is shaped by haplotype, with the Senegal haplotype associated with the mildest and the Bantu with the most severe clinical course (35). It is not yet clear whether haplotype affects the course of SCT, but haplotype may influence the risk for ECAST, especially since some of the “protection” via the Senegal haplotype comes from higher levels of fetal hemoglobin (2).

The coexistence of SCT with alpha thalassemia may be important also. In SCT, each red cell typically has approximately 40% hemoglobin S (HbS) in the absence of alpha thalassemia. However, the red-cell HbS concentration falls in concert with the number of alpha genes deleted (38). Up to one-third of African-Americans with SCT also have some form of alpha thalassemia. Their lower red-cell HbS reduces the propensity of those cells to sickle and may lower the risk of ECAST (23,32). So alpha thalassemia may be a “life-guard” in athletes and soldiers with SCT.

Other factors also may lower the threshold for ECAST. Asthma exacerbates acute chest syndrome and increases morbidity in children with sickle cell anemia (6). It seems possible that uncontrolled asthma or exercise-induced bronchospasm could contribute to ECAST. It is our clinical impression that exercise-induced asthma seems overrepresented in ECAST deaths in football and basketball conditioning.

Cofactors may predispose those with SCT to experience splenic infarction when not at altitude. Of the approximately 12 such cases in the literature, reported cofactors (besides SCT) include infectious mononucleosis and, more commonly, hereditary spherocytosis (HSO) (37,39). Just as splenic infarction at sea level may involve a “confluence of cofactors,” ECAST too may involve not mono or HSO, but a confluence of cofactors.

Supplements also may be cofactors in ECAST. When the normal exertional surge of epinephrine is combined with an exogenous stimulant, e.g., synephrine, it may tilt the athlete with SCT toward ECAST. This could apply in the case of a 22 year old obese, but otherwise healthy, active-duty, African-American sailor with SCT who was diagnosed initially with ER and heat illness. Unknown to the providers, he had been taking a synephrine-containing supplement for weight loss. After a brief hospitalization during which his CK peaked at 14,070 IU/L−1, he was discharged with CK not yet normalized but with preserved renal function. Several weeks later, he participated in the Navy Physical Readiness Test without medical clearance. Still unknown to providers, he had continued the dietary supplement for 3 months. While running, he experienced a second episode of a more severe heat illness and rhabdomyolysis. He developed hypovolemic shock, respiratory failure, renal failure, and DIC with severe, acute, ischemic muscle necrosis. Within 24 h, his CK reached a peak of 2.8 million IU/L−1. He survived despite experiencing permanent physical disabilities from muscle necrosis, compartment syndromes, and bilateral fasciotomies (8). Hence a variety of supplements theoretically could alter the local cellular environment and act as a contributor to ECAST.

ECAST Recognition and Treatment

At a 2011 summit sponsored by the American College of Sports Medicine and the Uniformed Services University Consortium for Health and Military Performance, consensus recommendations for effective ECAST emergency action plans were created (34). Based on the collaborative work of experts in the field, the guidelines include a chain of survival management algorithm and highlight the critical importance of direct communication with the receiving emergency department. The possibility of ECAST must be conveyed early to the receiving ED physician. ED management of ECAST consists of aggressive fluid and electrolyte management, blood gas monitoring to rule out metabolic acidosis, cardiac monitoring to identify onset of lethal arrhythmias, and dialysis to control hyperkalemia if present (34) (Fig. 2).

Prevention

Newborn screening programs in all 50 states and the District of Columbia include screening for sickle cell hemoglobin, so the presence of SCT is known early. However, the finding of SCT is not conveyed to the parents always and may be difficult to access when the athlete later enters the military or college (16). In 1991, the Army discontinued universal screening at entrance processing stations for military accessions in preference of universal precautions in training, including the following: careful attention to hydration, progressive heat acclimatization, and graduated conditioning and training (34). Conversely the Navy, Marine Corps, Coast Guard, and Air Force continue to screen for SCT (21), even though they are required no longer to do
so, per Secretary of Defense memorandum (14). Actions following screening are diverse, ranging from no action to informational brochure education and to face-to-face physician-patient counseling. In addition, in some basic training environments where screening is required, trainee warfighters are identified as SCT positive with unique armbands or belts, while in other settings, there is no individual identification but a focus on universal precautions. Similar to the military, while the NCAA mandates SCT screening for athletes, there is no standardized medical counseling or universal preventive interventions for SCT positive athletes. While some training modifications have been proposed for athletes with SCT, these are based on expert consensus, and although early results in division I football are quite promising, not enough time has passed to prove statistically that these precautions clearly are reducing ECAST deaths (17,18).

Important similarities in epidemiology between ECAST and other forms of ERD in young athletes can focus prevention efforts. It is postulated from studying the cases that most ECAST in the military occurs in basic training and most ECAST in division I football occurs in preseason.

conditioning, on day 1 of summer camp, or after coming back from a vacation or injury. Hence, preventive measures should be paramount during these periods. Adherence to heat, hydration, and exercise acclimatization practices is recommended for all athletes, including those with SCT. Proposed recommendations also include avoidance of timed serial sprints or miles, sprints beyond 500 m, and repeated exertion with limited recovery between cycles during the first 2 wk of conditioning (15,34).

Warfighters who have difficulty completing 1- to 2-mile timed runs or difficulty running after strenuous field exercises may be at particularly high risk for EHI. To avoid cumulative heat strain, they should be provided the ability to “heat dump” periodically (air conditioning exposure, cool showers, and rest in shaded areas). High levels of exertion and heat exposure alone or in combination with other risk factors such as prior or current illness, insufficient sleep, medications, supplements, and lack of acclimatization and/or physical conditioning all can exacerbate thermal strain and perhaps predispose an individual to an ECAST event (34).

**Way Ahead**

The literature is currently clear that while ECAST is uncommon, it is a real event that affects those involved in athletics and military service, often with tragic results. Improved surveillance and information gathering are essential to educate future trainers and medical providers on how athletes and warfighters with SCT should be monitored, to lead ECAST prevention and treatment efforts, and to provide better understanding of the “perfect storm” of associated factors that precipitate this perplexing phenomenon. Accordingly, various prospective registries of athletes with SCT are underway or being planned. In addition, genetic studies are currently in development to explore the possibility of genetic cofactors that either may contribute to or may confound ECAST.

Clearly we still have more questions than answers on ECAST. While SCT screening is endorsed uniformly at birth by all researchers and experts in this area with intent to lead ECAST prevention and treatment efforts, and to provide better understanding of the “perfect storm” of associated factors that precipitate this perplexing phenomenon. Accordingly, various prospective registries of athletes with SCT are underway or being planned. In addition, genetic studies are currently in development to explore the possibility of genetic cofactors that either may contribute to or may confound ECAST.

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