Sickle Cell Trait and Exertional Rhabdomyolysis

Michelle A. Cleary PhD, ATC • Florida International University

In contrast to the severe, often life-threatening complications of sickle cell disease, sickle cell trait has conventionally been considered a relatively benign condition. Questions have been raised, however, about whether otherwise healthy athletes or physically active individuals with sickle cell trait have a higher risk of sudden death associated with extreme exertion. A growing number of case reports of unexplained sudden death associated with physical exertion in previously healthy individuals with sickle cell trait have appeared in the medical literature over the past 3 decades.[1,2] Although the evidence about this complication associated with severe exercise is still incomplete and largely anecdotal, it seems likely that it can contribute to the development of exercise-related collapse, exertional rhabdomyolysis, and subsequent death.[1] This column briefly describes the conditions of sickle cell trait and exertional rhabdomyolysis, summarizes the evidence in the medical literature, and provides athletic trainers and therapists information for identifying individuals who might be at risk for sudden death as a result of maximal exercise.

Sickle cell trait results from inheriting a gene for hemoglobin A from one parent and for hemoglobin S from the other, resulting in the AS phenotype. People with sickle cell trait have no anemia and are considered healthy. Physicians have known for years, however, that among such individuals, exposure to prolonged hypoxic conditions such as at high altitude can cause sickling of the red blood cells in the renal medulla and spleen, resulting in complications that can lead to death.[1,2] For the vast majority of the 8% of the Black population in the United States who have sickle cell trait, the evidence suggests that it is a benign condition that, with rare exceptions, has no adverse effect on health.[2,3] Nonetheless, despite reassurances that sickle cell trait is generally compatible with athleticism, recent reports suggest a grave hazard for some people with sickle cell trait who charge recklessly into maximal exercise to which they are unaccustomed.[1] Severe exertion can lead to rhabdomyolysis and acute renal failure. In some cases, dehydration can be a precipitating factor in the development of sickling in muscle capillaries.[4]

Important questions remain about the risk to individuals with sickle cell trait, combined with a certain degree of dehydration and "heroic" effort, of developing sickling in the muscle capillaries, leading to muscle infarction and rhabdomyolysis.[1,4] Exertional rhabdomyolysis is associated with skeletal-muscle damage and release of myoglobin and intramuscular enzymes into the blood as a result of strenuous exercise. Myoglobin, other intramuscular proteins (particularly creatine kinase), and ions (particularly potassium) continue to spill into the bloodstream and can progress through a cascade of events that eventually lead to renal failure and even death.[5]

Because of the number of cases of sudden fatal or severe illness during exertion, the sickle cell trait is increasingly being regarded as a risk factor for sudden death during exertion. Eichner[1] has identified 30 cases of death associated with severe exercise reported in the medical literature since 1970. Twenty of these cases involved recruits in military training who were previously healthy but collapsed and died while exercising, particularly during running activities. The other 10 cases involved college athletes or active people who collapsed after maximal exertion. Some of the athletes had been exercising in hot weather; others were new to the altitude. Many were unaccustomed to the intensity level of the exercise, the heat, or the altitude and collapsed on the first or second day of football practice.[1,3] Most of these individuals had exertional rhabdomyolysis, heat stroke, or heat stress with acute renal failure, and several died before diagnostic evaluations were completed.[3,4]

From 1977 to 1981, the rate of sudden, unex-

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plained death in Black military recruits with sickle cell trait was 28 times higher than for Black recruits without sickle cell trait and 40 times higher than for all other recruits.[3] Although in the military, where records are centralized and relatively complete, 1 in 3,200 Black recruits with sickle-cell trait died suddenly without a known cause, the deaths occurred during or after considerable physical exertion associated with basic military training.[3] Because there appears to be a high relative risk of sudden death in physically active Black individuals with sickle cell trait, appropriate precautions might be indicated for athletes with sickle cell trait who engage in strenuous physical exertion, particularly at high altitude or in extreme heat.[1,2] It is noteworthy that studies of Black football players have shown a frequency of sickle cell trait not significantly different from that in the Black population in general, indicating no evidence of a negative selection factor resulting from sickle cell trait in this strenuous sport.[5]

Athletic trainers and therapists should be aware that many of these cases of exercise-related death have similar characteristics that potentially could be used to prevent adverse events. In general, the pattern of collapse appears to be similar in individuals who die "suddenly" and who have sickle cell trait. In most reported cases, the deaths seem to fit a similar pattern: collapse while running, sometimes at altitude, sometimes for very short (300–800 m) distances lasting less than 3 min, and almost always at maximal intensity.[1,4] The sequelae that follow are almost always characterized by metabolic acidosis, myoglobinuria, hyperkalemia, elevated plasma enzymes, renal failure, and "sudden" death within about 48 hr. This condition is different than classic exertional heat illness in that some cases occurred in ambient conditions that were rather mild (70 °F and 15% relative humidity), and in some cases, rectal temperature was relatively low (38.3 °C, or 101 °F, or less).[1,4,6]

Although there might be an important, yet-unidentified subgroup of individuals with sickle cell trait who have a genetic or other factor that predisposes sickling in muscle as a result of maximal exercise, athletic trainers and therapists must be aware that individuals with sickle cell trait can be at risk for severe exercise-related problems. For these individuals, the primary risk factors for developing exertional rhabdomyolysis include exercising at high intensities, in the heat/humidity, or at altitudes to which they are unaccustomed; exercising while dehydrated; exercise-induced asthma; and preevent fatigue caused by illness or lack of sleep.[1,6,7] Keep in mind that not all individuals with sickle cell trait are Black. Eichner[1] reported that a White high school boy who recently moved to Albuquerque, a city at high altitude, collapsed with abdominal pain and had sickle cell trait.

Knowledge of an athlete's sickle cell trait status is paramount in identifying at-risk individuals, minimizing high-risk activities for these individuals, facilitating early recognition of this exercise-related problem, and allowing prompt treatment. For individuals with sickle cell trait who might be more susceptible to or at higher risk for problems related to severe exercise, it would be reasonable and prudent to have an extra layer of awareness and to "increase your radar" so that necessary precautions can be implemented. For all athletes, one of the most important precautionary measures that must be enforced by coaches and athletic trainers and therapists is gradual preseason conditioning and acclimatization in preparation for the first day of practice. All athletes, with or without sickle cell trait, should train wisely, stay hydrated, modify activity based on environmental conditions, and enter novel exercise intensity with gradual progression. Without precluding participation for athletes with sickle cell trait, preventing potentially life-threatening complication of severe exercise in these individuals requires education, awareness, identification of at-risk or susceptible individuals, and good clinical judgment.

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Michelle Cleary is director of Advanced Athletic Training/Sports Medicine at Florida International University in Miami.