Sickle Cell Trait

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Sickle cell trait can pose a grave risk for some athletes. In the past few years, exertional sickling has killed nine athletes, including five college football players in training. Exercise-physiology research shows how and why sickle red cells can accumulate in the bloodstream during intense exercise bouts. Sickle cells can “logjam” blood vessels and lead to collapse from ischemic rhabdomyolysis. Diverse clinical and metabolic problems from explosive rhabdomyolysis can threaten life. Sickling can begin in 2-3 minutes of any all-out exertion, or during sustained intense exertion — and can reach grave levels very soon thereafter if the athlete struggles on or is urged on by coaches despite warning signs. Heat, dehydration, altitude, and asthma can increase the risk for and worsen sickling. This exertional sickling syndrome, however, is unique and in the field can be distinguished from heat illnesses. Sickling collapse is a medical emergency. Fortunately, screening and precautions can prevent sickling collapse and enable sickle-trait athletes to thrive in their sports.

This article on sickle cell trait keys mainly on the features of exertional sickling and how to distinguish it from heat illnesses and other causes of collapse. Some cases of exertional sickling in athletes, especially in football, have been confused with heart disease, viral meningitis, heat cramping, or heat stroke.¹ Knowing the setting and distinguishing features of exertional sickling is vital to athletes, coaches, athletic trainers, and team physicians, because sickling collapses and deaths can be prevented with screening and precautions.

The sickle gene is common in people who come from where malaria is widespread, such as Africa. Over the millennia, carrying one sickle gene—sickle cell trait—fended off death from malaria, which resulted in one in 12 African-Americans (versus one in 2,000 to one in 10,000 White Americans) with sickle trait.

In the past four decades, exertional sickling has killed more than a dozen football players in training and many more military recruits in boot camps. In the past 6 to 7 years alone, sickling has killed nine athletes with sickle trait: five college football players in training, two high school athletes (one a basketball player), and two 12-year-old boys training for football.² Other recent non-fatal cases are known to exist. For example, one college football player was fortunate to survive sickling; he underwent renal dialysis for two weeks and was hospitalized for two months. Among 136 well-studied, sudden, non-traumatic, sports deaths over a decade in high school and college athletes, seven (5%) were from sickling-associated rhabdomyolysis.³

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The U.S. military was the first to tie sickle trait to sudden death during the physical training of recruits. The relative risk of exercise-related death in sickle trait, unexplained by preexisting disease, was about 30. The risk plummeted, however, for career military after basic training. This observation led researchers to speculate that the risk of exercise-related death in sickle trait is mainly during intense conditioning to novel exercise or during sustained exertion for which the recruit is unprepared.4,5

Analysis clarified the type of death. Most collapses occurred as recruits ran 1 to 3 miles. Of 40 deaths or near-deaths from sickling collapse, some had features suggesting heat illness (but not heat stroke) and others were sudden cardiac arrhythmic death. But most deaths were delayed for hours or a day or two and were from metabolic complications of rhabdomyolysis and myoglobinuric renal failure. Indeed, acidosis and hyperkalemia from explosive rhabdomyolysis may have caused the sudden arrhythmic deaths. So the main cause of death is explosive rhabdomyolysis, and the risk of rhabdomyolysis is about 200 times greater in military recruits with sickle trait.4,5

Pathophysiology of Exertional Sickling

Exercise physiology helps explain why exercise in sickle trait can cause rhabdomyolysis. In sickle trait, in which about 40% of hemoglobin in each red cell is hemoglobin S, strenuous exercise evokes four forces that foster “sickling,” or change of red-cell shape (when the red cell releases its oxygen) from round to quarter-moon or “sickle.” The metabolic acidosis and hyperthermia “shift to the right” the oxygen dissociation curve, displacing more oxygen from hemoglobin S. Dehydration of red cells traversing the hyperosmotic milieu of working muscles increases the concentration of hemoglobin S. And severe hypoxemia because of extreme muscle oxygen uptake completes the sickling foursome.

Military researchers showed that sickle cells accumulate in venous blood draining exercising muscles and in blood from the arm in recruits cycling with the legs. When sickle-trait recruits cycled at high altitude, sickle cells in venous blood from the forearm rose to a mean of 9% and a maximum (in one man) of 28%. This suggests that as exercise stress and hypoxemia increase, sickle-trait athletes can accumulate sickle cells in the arterial circulation—sickle cells that can go to the heart, brain, and muscles.6 If too many sickle cells accumulate, they can “logjam” blood vessels and rob vital organs of blood.

Recent research finds that dehydration can increase exertional sickling. Two men with sickle trait walked briskly for 45 minutes in the heat, once with fluids to offset sweat losses and once without fluids. Without fluids to offset dehydration, sickling (in forearm venous blood) increased steadily to peaks of 3.5% and 5.5%.7

Field Studies in Africa Suggest a Pattern

Field studies in Africa suggest that elite sickle-trait runners are limited not in single sprints but in middle-distance, semi-marathon, and altitude racing. In Ivory Coast, 13 sickle-trait runners won 33 titles, but only one was at 800 meters or more. The other 32 wins were all in races of 400 meters or less.8 Sickle-trait racers were
underrepresented among top finishers in a semi-marathon and underperformed in high-altitude stretches of a distance race.\textsuperscript{9,10} In contrast, sickle-trait runners can be elite sprinters.\textsuperscript{11} However, these same African field studies suggest that sickle trait can limit racing performance at altitude or at 800 meters and beyond. This pattern seems to hold in training for American college football, where repeated sprints that total about 800 meters or beyond seem to pose a sickling hazard.

**Sickling Collapse: College Football**

The first sickling death in football was in 1974, a Black defensive back from Florida who collapsed two years in a row on the first day of practice at altitude in Colorado.\textsuperscript{2} The first year, he survived. The second year, aiming to finish the first conditioning sprint (880 yards), he fell behind his group after 660 yards, staggered forward a bit, then fell at the edge of the track. He complained of severe leg pain. The next day, he died in the hospital with “severe acidosis” and “severe sickling in the kidneys.”

The pattern of the most recent death, a freshman defensive back at Rice University, is similar. In the fall of 2006, he ran 16 sprints, each 100 yards, and said he felt bad and his legs hurt. Within minutes, he collapsed and became less responsive. No cardiac arrest occurred. He was rushed to a hospital. Serum creatine kinase rose sharply and overnight his kidneys failed. He died the next morning, likely from cardiac arrhythmia from hyperkalemia. The cause of death was acute exertional rhabdomyolysis associated with sickle cell trait.

It seems that at least 13 college football players have died after a sickling collapse, and although the type and proximate cause of death in some have been debated, the setting and syndrome in most are similar. Sickling football players may be on field only briefly, sprinting only 800 to 1600 meters, early in training, often the first or second day of preseason workouts. Sickling can also occur during repeat hill, ramp, or stair running, or even during intense, sustained weight-lifting or other grueling resistance drills, such as pushing a weighted sled in the “bear-crawl” position. Sickling collapse can occur if the tempo increases late in intense one-hour football drills, including “mat drills” in the winter. At the end of a long, hot football practice, if players run sprints or “gassers” with insufficient breathers, sickling can begin within 600 meters. Sickling can even occur rarely in the game, for example, when a running back is in almost constant action during a long, frantic drive downfield.

**Other Sickling Situations**

Sickling collapse is not limited to college football. It has killed or nearly killed several college or high school basketball players (two were females) in training, typically when “running for time,” such as repeat sprints on the court (“suicide runs”), laps on a track, or a long training run. A young sickle-trait runner collapsed twice at the end of cross-country races. He survived severe rhabdomyolysis and renal failure.\textsuperscript{12}

The harder and faster athletes go, the earlier and greater the sickling. That is why sickle collapse occurs sooner (at a shorter distance) in top college football players sprinting all-out (their “drop zone” is often 800 to 1200 meters) than in military
recruits running 1 to 3 miles. Some sickling can begin in only 2 to 3 minutes of sustained sprinting—or in any other sustained all-out exertion—and sickling can soon increase to grave levels if the stricken athlete struggles on or is urged on by the coach to push beyond pain and weakness. Any cramping, struggling, wobbling, or collapse in a sickle-trait athlete must be considered sickling—a medical emergency—until proved otherwise. Especially in high heat and humidity, the exertion need not be “all-out” to cause ominous sickling, as in military men who collapse at the end of a 2-mile fitness run.4

Heat and dehydration increase the risk of sickling, mainly because they make the drill more difficult and drive the blood oxygen lower. They also tend to worsen sickling, by shifting the oxygen-dissociation curve to the right and by increasing the concentration of hemoglobin S. Exercise-induced asthma and the thin air of altitude also increase sickling, even when the exercise is not all-out, because of lower blood oxygen.

**Differential Diagnosis: Four Possibilities**

This is key for athletic trainers and team physicians to know: If an athlete takes the field in good health, the four most common nontraumatic causes of sudden exertional collapse are a cardiac condition, a heat illness, asthma, or sickling. Clues can help observers distinguish among these four emergencies. In general, cardiac collapses are very sudden and without cramping and, especially with ventricular fibrillation, when the athlete hits the ground, he no longer talks and may even have seizure activity. Exertional asthma typically presents with a slow crescendo of chest tightness and undue breathlessness, sometimes with audible wheezing, usually without extremity or back pain or cramping.

It seems that sickling collapse on field is most often confused with heat cramping, heat exhaustion, or heat stroke. However, unlike heat exhaustion or heat stroke, sickling collapse often occurs early in a workout, in the first few minutes, as during wind sprints. The point is, the athlete has not been out in the heat long enough to suffer heat stroke. Rectal temperature is generally elevated only mildly and in concert with the activity. Also, with heat stroke, central nervous system changes are more profound and can range from confusion to delirium to stupor, seizures, or coma. The most telling symptom of sickling collapse is increasing pain and weakness in the working muscles, especially the legs, buttocks, and/or low back. The athlete may call the pain “cramping,” but it is unique. Knowing which athletes have sickle trait avoids possible confusion over “cramping.” Any cramping is considered sickling until proved otherwise.

Football players who have suffered both heat cramping and sickling can tell the difference between the two syndromes. Notable differences are the following:

1. Heat cramping often has a prodrome. Hours or minutes before the athlete suffers heat cramping, he may see or feel twitching or twinges in tired muscles, those destined to cramp. The athlete who knows heat cramps will tell you, “They are about to come on.” In contrast, sickling has no prodrome.
2. The pain is different. Heat-cramping pain is an excruciating pain of sustained, full contraction of muscles, a “lock-up.” Sickling pain is milder, neither the
unbearable pain of a heat-cramp lock-up nor the “burning” pain in the thighs as at the end of a middle-distance race. Sickling pain is an ischemic pain from trying to use muscles robbed of blood supply—it is like the pain of intermittent claudication when leg arteries are narrowed by atherosclerosis.

3. What stops the athlete is different. With heat cramping, athletes “hobble to a halt”—the fully contracted muscles no longer work. With sickling, athletes “slump to a stop”—the legs become “weak and wobbly” and no longer hold them up.

4. The physical findings are different. In major heat cramping, one can see and feel large, rock-hard muscles in full contraction, and the athlete often is writhing and yelling in pain. With sickling, the exhausted player lies fairly still and complains little, except to say that he feels bad and his legs hurt and are weak. The muscles look and feel normal.

5. The response is different. After 10 to 15 minutes sitting in a cold tub, drinking fluids and getting supplemental oxygen by face mask, the athlete with mild sickling “feels fine.” This is likely because many sickle cells have reverted to normal as they regained oxygen. In contrast, major heat cramping often takes an hour or two to resolve, even in a player resting in the training room, being treated with stretching, massage, and intravenous fluids.

In our experience in college football, most but not all sickle-trait athletes sooner or later will have problems, mild or severe, from exertional sickling. The risk may vary not only with the amount of hemoglobin S in each red cell, but also with the sport, setting, drill, or fitness. Nor will all sickling athletes describe this syndrome the same way or look exactly the same. Some present with leg and low-back pain or “leg cramps” that “spread up through my body.” Some complain of leg weakness more than pain. Some say “my chest muscles are tight” or “I just don’t feel right” or “I can’t catch my breath” and simultaneously say their legs are weak or “wobbly.” They can be on hands and knees by this point, breathing very fast, with great anxiety. Some stoic players with sickling will just stop and sit or lie down, saying “I can’t go on” or “my legs won’t go.” This self-limiting feature has likely saved the lives of many sickle-trait athletes.

**A Medical Emergency**

A sickling collapse is an emergency. Fast action can save a life:

- Check vital signs.
- Give supplemental oxygen by face mask.
- Cool the athlete, if necessary.
- Failing immediate improvement, call 911, attach an AED, and start an intravenous line.
- Get the athlete to the hospital quickly.
- Tell the doctors to expect explosive rhabdomyolysis and its grave metabolic complications.
Return to Play

Return to play must be individualized. Some athletes who spend a long time in the hospital with major, debilitating rhabdomyolysis and renal failure do not return to play. For example, the college football player who spent two weeks on renal dialysis and two months in hospitals was not cleared to return to play because of permanent loss of renal function. At the other extreme are exercising athletes who report early symptoms of sickling and are attended to immediately with rest, oxygen, and cooling. In our experience, these athletes can rebound quickly. Likely many or most sickle cells revert quickly to normal shape as they traverse the lungs and can feel normal again in 15 to 30 minutes. We have let such athletes return to play the next day.

Many athletes may fall between these two extremes. This has been the case for football players who develop moderate rhabdomyolysis. Indeed, we have seen troubling myonecrosis of lumbar paraspinal muscles, with a sharp rise in creatine kinase (sometimes to the range of 10,000 to 50,000 IU/L) but no worrisome rise in creatinine and no renal compromise. These athletes tend to have limiting muscle weakness and soreness for a week or two and need daily assessment to ensure prudent, gradual return to play.

Preventive Measures

How to prevent sickling collapse is detailed elsewhere; in general, it involves screening and simple precautions. Over the past decade, dealing with 13 sickle-trait college football players and lesser numbers of basketball players and track athletes, these precautions seem to work for us:

- Build up slowing in training, slow the tempo, and give longer “breathers.”
- Allow no timed sprints or miles.
- Allow no sprints beyond 500 meters.
- Allow no all-out exertion of any kind for 2 to 3 minutes without a breather.
- Adjust work/rest cycles for heat, hydrate well, control any asthma, and allow no workout if ill.
- Have supplemental oxygen ready at altitude games.
- Set the tone so athletes report symptoms immediately and coaches and athletic trainers consider any struggling or cramping as sickling.
- If sickle-trait athletes can set their own pace, they seem to do well.

Screening and precautions for sickle cell trait can prevent sickling collapses and deaths and enable sickle-trait athletes to thrive in their sports.

References