Sickle Cell Trait and Sudden Death—Bringing it Home

Bruce L. Mitchell, MD
Jacksonville, Florida

Sickle cell trait continues to be the leading cause of sudden death for young African Americans in military basic training and civilian organized sports. The syndrome may have caused the death of up to 10 college football players since 1974 and, as recently as 2000, was suspected as the cause of death of three U.S. Army recruits. The penal military-style boot camps in the United States and the recent death of two teenagers with sickle cell trait merits renewed vigor in the education of athletic instructors, the military and the public about conditions associated with sudden death in individuals with sickle cell trait.

Key words: exercise ■ hypoxia ■ sickle cell trait ■ sudden death

 From the Division of Community Internal Medicine, Mayo Clinic Jacksonville, FL. Send correspondence and reprint requests for *J Natl Med Assoc.* 2007;99:300–305 to: Dr. Bruce L. Mitchell, Division of Community Internal Medicine, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224; e-mail: mitchell.bruce@mayo.edu

A great deal of controversy continues to surround sickle cell trait and its association with exercise-related morbidity and sudden death. Sickle cell trait has a high prevalence among African Americans, and although most individuals have minimal or no clinical sequelae, debate centers on the effects of extreme physical exertion, dehydration and relative hypoxia (typically at high altitudes). The large number of African Americans who are enlisted in the U.S. military or who participate in endurance athletics are particularly at risk, and their experiences support the characterization of this condition as a public health problem. This paper describes risks and the complex interaction of physiologic and sociologic factors involved in downplaying the clinical significance of sickle cell trait. Screening and clinical recommendations are made that will identify and improve the care of individuals with sickle cell trait.

Sickle Syndromes

Sickle syndromes include several distinct diseases that cause red blood cells to sickle in vivo. The most recognized are sickle cell anemia, sickle cell trait, hemoglobin sickle cell disease and sickle cell-ß-thalassemia. In the United States, of all the hemoglobinopathies, individuals with homozygous sickle genes (Hgb SS) have the greatest morbidity and mortality, and the disease limits their ability to participate in athletic activities. Sickle cell trait is the heterozygous condition (Hgb AS) and has a prevalence rate of 8% in African Americans and 0.046% in nonblack Americans.

When sickle hemoglobin is deoxygenated, the molecules have an increased tendency to form hydrophobic bonds and will subsequently aggregate into large polymers on the red blood cell membrane. The rate and extent of polymer formation are dependent on three factors: intracellular hemoglobin concentration, presence or absence of Hgb F and the degree of oxygenation in the cell. In sickle cell trait, the hemoglobin concentration is normal, and Hgb F is not usually present postnatally. Therefore, the predominant physiologic cause of intravascular sickling in those with heterozygous sickle genes (Hgb AS) is the low level of oxygenation in the cell.

Sickle Cell Trait and Exercise

During exercise, the pH decreases and the temperature increases at the tissue level to facilitate oxygen delivery; these changes lead to higher concentrations of deoxygenated hemoglobin. Under usual circumstances, cardiac output is likely to increase substantially and raise perfusion pressure sufficiently to overcome local tissue hypoxia and avoid the membrane polymerization that can occur with sickle cell trait. Although no study has shown sickling during rest at sea level, maximal exercise at sea level routinely produces mild intravascular sickling (typically <1%).[1,2] Venous blood from an exercising limb was measured and showed that sickling does indeed occur at low altitude (1,270 m); the sickling rate dramatically increased at high altitude (4,000 m). Even though multiple studies showed that large amounts of sickled cells formed during exercise, no measurable effects on exercise performance were noted.[3,4] Nevertheless, the formation of sickled cells supports a causal relationship between sickle cell trait and exercise-relat-

ed complications. The wide range of sickling that occurred during peak exercise (1–25%) suggests that other physiologic variables play a role.

Sickle Cell Trait and Sudden Death

The strongest evidence implicating intravascular sickling with tissue injury and even death is extreme exercise, typically to exhaustion, with dehydration and relative hypoxia (altitude). The first cases identified were four U.S. Army recruits who died during or immediately after strenuous exercise during basic training at Fort Bliss, TX (elevation 4,050 ft) between March 1968 and February 1969.[5] On the basis of autopsy specimens and morphologic criteria previously established for individuals with sickle cell disease,[6,7] the authors concluded that the soldiers died of diffuse microvascular obstruction from sickled erythrocytes, or "sickle crisis." Although hypoxemia was modest at 4,000 ft (ambient PO_2, 70–75 mmHg), investigators concluded that the decrease in arterial PO_2 levels initiated events that led to acidosis, excess lactate and intravascular sickling. They postulated that even though factors such as dehydration, increased blood viscosity and hypercoagulability may have contributed to the syndrome, the "... moderate-to-severe exercise after recent arrival at a relatively high altitude ..." ultimately led to sickle crisis and sudden death. They also concluded that the variable Hgb S concentration (30–44%) among recruits spared some with sickle cell trait but not others.

Since the description of the initial deaths, multiple reports of serious complications or sudden death during exercise for individuals with sickle cell trait have been published.[8-21] The magnitude of the problem was established after a retrospective review of all deaths among active-duty military between 1977–1981 was published by Kark et al[22] in 1987. The comprehensive review, written by Army Medical Corps physicians, concluded that the risk of sudden unexplained death in black recruits with sickle cell trait was approximately 30-fold more than that of black recruits without sickle cell trait and 40-fold more than that of nonblack recruits. Most deaths occurred during the first month of training and were associated with exertional activities requiring maximal effort. Much of the data implicated exertional heat illness, which had been somewhat arbitrarily subclassified into heat stroke, heat exhaustion and heat injury. Deaths were attributed to exertional rhabdomyolysis if muscle necrosis was a major component of the clinical picture.[19,23-25] The degree of hyperthermia present during any of the syndromes was variable, and it was not always present during exertional rhabdomyolysis. Furthermore, in many cases, the true cause of death was difficult to determine; rhabdomyolysis may have been attributable to exercise, or mild muscle necrosis may have been augmented by hypotension during resuscitative measures and cardiac arrest.

Several factors may explain the higher incidence of sudden death in military recruits with Hgb AS when compared with civilian athletes. The intensity of physical conditioning over an 8–12-week period is often implicated, and conditioning typically includes activities that raise the metabolic rate 10–14 times above the basal level. Other commonly cited factors included variable recruit conditioning, viral syndromes, water deprivation in the field and heavy protective military gear that may inhibit evaporation of sweat.

An age-associated increase in the death rate has been noted for those with sickle cell trait;[22,26] the death rate of 28–29-year-olds is eight-fold higher than that of 17–18-year-olds. The higher death rate may be attributable to the cumulative effects of renal papillary necrosis and resultant isosthenuria (Figure 1),[27] the inability of the kidneys to maximally concentrate urine. Isosthenuria is the only clinical condition consistently present in individuals with sickle cell trait; the condition tends to be intermittent and reversible initially but gradually may become structural, irreversible and cumulative.[28,29]

Even though the majority of data in the sickle syndrome literature[5,6,8,9,12,14,16,22,30,31] showed that sickle cell trait was associated with increased risk of exercise-induced sudden death (independent of pre-existing disease), the inability to discern histologically artifactual postmortem sickling from antemortem sickling has left the association open to debate. Even though a causal relationship is plausible, no direct evidence links the pathogenesis of exercise-related deaths to microvascular obstruction by rigid erythrocytes.

In the context of their study findings, in 1982, the Army Medical Corps reiterated the importance of regulations to decrease the incidence of exertion-related deaths and noticed a dramatic decrease in the death rate in individuals with sickle cell trait over the next 10 years.[32] Each branch of the military has developed its own policy. In 1996, the Army ceased screening for the sickle gene. The Marines screen all individuals and do not alter the routine of those with sickle cell trait. The Air Force screens everyone and offers the option to decline service to each recruit positive for the sickle gene. The Navy screens recruits and identifies those with sickle cell trait by a neck tag and a red belt during strenuous exercise drills. The Army was said to be reviewing its policy with respect to screening after eight deaths occurred during basic training from 1999–2000.[32] Of those soldiers, five were tested and three were positive for the sickle gene. Their review has been put on hold since the start of the Iraq War. The Sickle Cell Disease Advisory Committee of the National Heart, Lung and Blood Institute (a section of the National Institutes of Health) has since recommended that the military stop the routine screening of recruits for sickle cell trait.

Bringing It Home

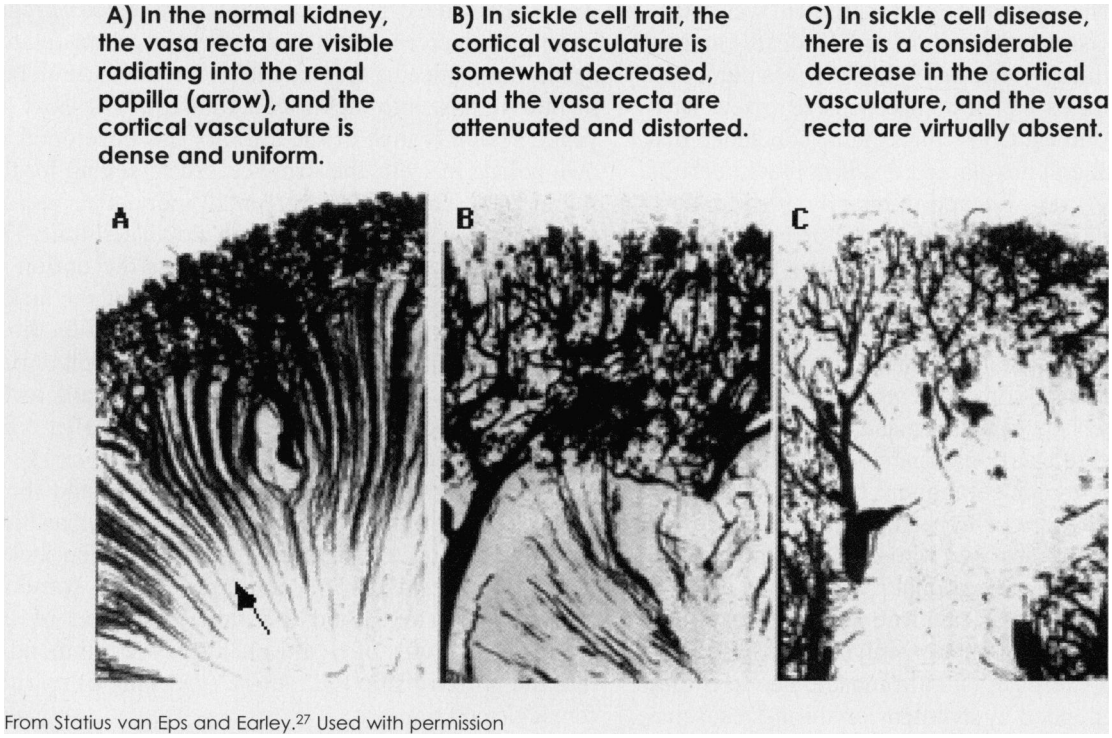
And that is where we are: inconclusive data have been accepted; inconsistent messages about screening, prevention and precaution have been relayed; and research into sickle cell trait-associated sudden death has not advanced. For many physicians, the story stops there. However, I am an African-American male with sickle cell trait, and this is a personal journey. In August 1975, I was a 17-year-old Navy recruit in basic training at the Recruit Training Center in Orlando, FL (Figure 2). I can easily recall the daily marches and drills on the "blacktop" in 105° weather. I can also recall the multiple near-syncopal episodes that, like most 17-year-olds, I tried to ignore so I would not appear weak in front of my fellow sailors. Were any of these episodes due to sickle cell trait and exertional heat illness? I will never know.

Before new regulations were implemented in 1982, the exercise-related death rate among black recruits with sickle cell trait was 30 times higher than that of black recruits without sickle cell trait.[22] Why did 13 years pass after the four deaths occurred in Fort Hood before the military implemented new regulations? Why is there still no consensus among practicing physicians on how to advise patients with sickle cell trait and their parents, athletic trainers and coaches? What roles have black scientists and physicians played in discouraging or supporting further research in this area?

I believe research has been hindered for several prevailing reasons. Many leaders in the black community were reluctant to support identification of increased actuarial risk, and several insurance companies had increased rates and refused to issue or renew policies for individuals with sickle cell trait, even when sickle cell trait was not considered an actuarial risk. My mentor, Dr. Louis Sullivan, wrote in 1987, "... there is no justification for discrimination in employment, job promotions, insurability, or other aspects of daily living among the 8 percent of the black population in the United States who have sickle-cell trait."[33] Moreover, the Health Insurance Portability and Accountability Act, enacted in 1996, prohibited issuers of health benefits from considering "genetic information" when evaluating, granting, denying or canceling an individual's healthcare coverage. Genetic information included results of genetic tests (e.g., a patient's Hgb SS or Hgb AS status) or findings of a routine history and physical examination.

Another barrier to investment in research has been the prevailing social climate in the United States during this period. Racial prejudice has undoubtedly fueled the occasional acrimonious debate. Combined with the inherent mistrust of medical research by many blacks, particularly in light of research fiascos such as the Tuskegee Syphilis Study and our recent acknowledgement of the pervasive disparities in healthcare, it is not

Figure 1. Injection microradiographs of kidneys from an individual with no hemoglobinopathy (A), sickle cell trait (B) and sickle cell disease (C). The renal cortex is at the top and the medullary pyramid is at the bottom of each picture.



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difficult to understand why the motives of anyone associated with the medical establishment are questioned.[34]

The unpredictable nature of events leading to sudden death is the main reason the true tenets of scientific method could not be consistently applied. Specifically, affected individuals need to be observed in extreme environments with all the implicated variables (e.g., increased ambient temperature, dehydration, poor conditioning, viral illnesses, etc.) to form a reasonable hypothesis. However, variability in the clinical presentation and environmental factors makes testing the hypothesis for validation nearly impossible.

After publication of the comprehensive review by Kark et al,[22] physicians generally accepted that indeed there was an increased risk of sudden unexplained death associated with physical exertion in individuals with sickle cell trait. Multiple prospective and well-controlled physiologic studies from the 1980s[3,33,35] showed that sickle cell trait alone was not an impediment to exercise tolerance or maximum performance. However, a subset of individuals with sickle cell trait obviously have an increased risk of exercise-induced complications. Most researchers and clinicians working in this area appear to have concluded that the increased morbidity and mortality for individuals with sickle cell trait result from the confluence of poor conditioning, strenuous physical exertion (especially in hot climates), dehydration and age.[22,26]

Previous studies showed that exercise to exhaustion produced some intravascular sickling at sea level,[1,2] and the amount of sickling was variable among individuals with Hgb AS.[3,4] In the absence of further evidence, we must conclude that Hgb AS and exercise-related sudden death have a cause-and-effect relationship. However, substantiation of that relationship is unlikely.

Making treatment decisions and recommendations on the basis of assumptions is not without precedent. For example, even though there has been considerable evidence for many years indicating that maintenance of euglycemia decreases most microvascular complications of diabetes mellitus (retinopathy, neuropathy and clinical nephropathy), there was no conclusive evidence that showed improved glycemic control decreased cardiovascular complications. The United Kingdom Prospective Diabetes Study[36] showed improved lipoprotein profiles with improved glycemic control, and the Diabetes Control and Complications Trial[37] did not show a statistically significant decrease in macrovascular events with improved glucose control. Nevertheless, clinicians assumed a cause-and-effect relationship between hyperglycemia and poor cardiovascular outcomes, and we continued to tell this to our patients and the public in the absence of conclusive data. Diabetic research progressed and only recently has confirmed that improved glycemic control decreases the risk of cardiovascular disease.[38]

Future Research

More attention needs to be given to the progressive and cumulative nature of the renal effects of sickle cell trait. Previous work[28,29] showed that after the fourth decade, some individuals with Hgb AS had the same diminished renal concentrating capacity as that of patients with Hgb SS (sickle cell disease), which created a clinical situation similar to nephrogenic diabetes insipidus (Figure 3).[27] Nevertheless, the prevalence and magnitude of renal dysfunction generally remain unknown. How does our lack of awareness and surveillance of renal concentrating capacity affect our ability to treat diseases such as systemic arterial hypertension and diabetes mellitus for patients with Hgb AS? In light of the potential for volume depletion, especially during physical exertion, is diuretic use ever appropriate in this population?

Under conditions of severe hypoxia, those with sickle cell trait are at increased risk of intravascular sickling. I designed a study to better understand the physiologic changes that occur in individuals with sickle cell trait while diving with a self-contained underwater breathing apparatus (SCUBA); ultimately, the goal was to calculate the risk of decompression sickness. The pilot study was funded for two years and was to test divers with sickle cell trait. Blood, drawn anaerobically and immediately fixed upon ascent from several depths, was to be evaluated for sickled red blood cells. After soliciting participation from major African-American dive organizations in the United States over several years, we were able to enroll only a few participants. The study was terminated because of lack of participation. Later discussions with potential participants revealed that most were concerned

Figure 2. Photograph of the author at the completion of Navy basic training (September 1975)

about the effect of adverse findings from the study restricting their ability to get diving insurance. Most also felt that since they had been diving thus far with no serious consequences, the possibility of intravascular sickling with diving was small or inconsequential.

CONCLUSION

All individuals who are phenotypically at risk should know their Hgb S status. In the absence of definitive studies that identify individuals with sickle cell trait who have the highest risk of sudden death, specific precautions should be reinforced. When participating in strenuous activities, care should be taken to avoid dehydration, and water must be consumed beyond the level of intake stimulated by thirst, especially in hot and humid conditions. Conditioning regimens should be slow and gradual, and older or obese individuals may need to take extra precautions. Activities requiring maximal exertion should be limited when the individual feels ill, and such activities should be limited for ≥1–2 weeks after viral syndromes or respiratory infections.

The military (and military-like institutions) should screen all recruits for the sickle gene and establish measures during basic training that would decrease the likelihood of exertional heat illness for all participants. These measures will decrease the disparity in sudden death between those with sickle cell trait and those with normal hemoglobin, and they would eliminate the need to mark and segregate individuals. Knowledge of a recruit's Hgb S status could facilitate prompt and appropriate treatment during a medical emergency. As individuals with sickle cell trait age and acquire other diseases (e.g., diabetes, hypertension, etc.), military physicians can better direct exercise and treatment regimens that are suitable for them.

Since diuretics play a major role in the treatment of hypertension in blacks, clinicians should be aware of the possible deleterious effects of this class of drugs for those with sickle cell trait. Patients with hematuria, polyuria or nocturia should be evaluated promptly.

Until further research is conducted, individuals with sickle cell trait who dive with SCUBA should limit their dives to <66 ft (2 atmospheres). They should also diligently maintain adequate hydration before and after dives.

African Americans clearly have a vested interest in understanding variables that increase the morbidity and mortality of this otherwise benign condition. New research initiatives need to be encouraged and broadly supported. We must understand the social context in which many previous studies were conducted and recognize its potential effect on further scientific research. Until conclusive data are gathered, the reasonable assumption of a causal relationship between sickle cell trait and higher morbidity and mortality must be acknowledged to develop consistent, cautionary recommendations for our patients, the military and the public.

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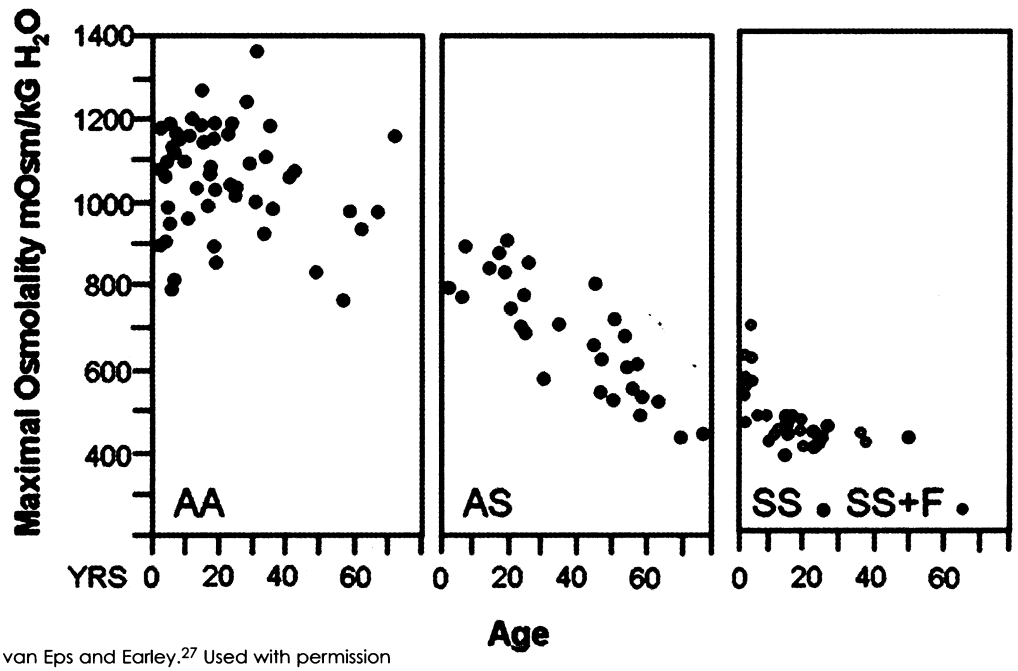
Figure 3. Relationship between maximal urinary osmolality and age in normal subjects (AA), sickle cell trait (AS), sickle cell anemia (SS, SS+F)



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