Challenging Return to Play Decisions: Heat Stroke, Exertional Rhabdomyolysis, and Exertional Collapse Associated With Sickle Cell Trait

Chad A. Asplund, MD, MPH, FACSM,*† and Francis G. O’Connor, MD, MPH, FACSM‡

Context: Sports medicine providers frequently return athletes to play after sports-related injuries and conditions. Many of these conditions have guidelines or medical evidence to guide the decision-making process. Occasionally, however, sports medicine providers are challenged with complex medical conditions for which there is little evidence-based guidance and physicians are instructed to individualize treatment; included in this group of conditions are exertional heat stroke (EHS), exertional rhabdomyolysis (ER), and exertional collapse associated with sickle cell trait (ECAST).

Evidence Acquisition: The MEDLINE (2000-2015) database was searched using the following search terms: exertional heat stroke, exertional rhabdomyolysis, and exertional collapse associated with sickle cell trait. References from consensus statements, review articles, and book chapters were also utilized.

Study Design: Clinical review.

Level of Evidence: Level 4.

Results: These entities are unique in that they may cause organ system damage capable of leading to short- or long-term detriments to physical activity and may not lend to complete recovery, potentially putting the athlete at risk with premature return to play.

Conclusion: With a better understanding of the pathophysiology of EHS, ER, and ECAST and the factors associated with recovery, better decisions regarding return to play may be made.

Keywords: return to play; heat illness; rhabdomyolysis; sickle cell trait

Sports medicine physicians are frequently relied on to make return-to-play (RTP) decisions for sports-related conditions and injuries. Many of these are musculoskeletal injuries that sports clinicians are well trained for, regularly encounter, are not life threatening, and feel comfortable managing. In addition, many orthopaedic as well as medical conditions have identifiable resources, such as the American College of Sports Medicine Team Physician Consensus Statement series, the Preparticipation 4th Edition Monograph, and the Bethesda Conference Guidelines, to assist the sports medicine provider with prudent RTP decisions. Occasionally, however, sports medicine clinicians are challenged with complex medical conditions for which there is little evidence-based guidance, and physicians are instructed to individualize treatment; included in this group of conditions are exertional heat stroke (EHS), exertional rhabdomyolysis (ER), and exertional collapse associated with sickle cell trait (ECAST). These entities are unique in that they may cause organ system damage capable of leading to short- or long-term detriments to physical activity and may not lend to complete recovery, potentially putting the athlete at risk with premature RTP.
EVIDENCE-BASED RETURN-TO-PLAY DECISION MAKING

Return-to-play decisions are the hallmark of a team physician’s clinical work.5,8 Ideally, the RTP decision would be directed by high-quality, patient-oriented evidence. However, there are many situations where the evidence is sparse or lacking and a general framework must be used to guide RTP decisions. The framework should consist of medical factors and sport-specific risk factors/modifiers and include elements that may modify decision making.29 Ultimately, each RTP decision must be individualized based on the specific facts and circumstances; however, there are some absolutes that must be satisfied before RTP is considered. First, near normalization of anatomic/physiological deficits, which may manifest as normalization of laboratory results or diagnostic testing or return of range of motion and strength in the affected limb, must be obtained. Second, the athlete must be psychologically ready for return to sporting activity. Third, sport-specific skills must be restored with or without equipment modification, orthosis, or bracing. Finally, risks to the athlete and other competitors must be appropriately mitigated so that return to sport does not pose an undue risk to the athlete or others.21 This process should be one of open communication between the athlete, physician, athletic trainer, parents, and others with a significant stake in the athlete’s return. When in doubt, it is best to make conservative decisions, keeping the athlete’s safety at the forefront. As demonstrated in subsequent discussions on EHS, ER, and ECAST, the assessment of normalization of anatomic/physiological deficits as well as the challenge of psychologic readiness for RTP become challenges for both the team physician and the athlete.

EXERTIONAL HEAT STROKE

Exertional heat stroke is defined as a multisystem illness characterized by central nervous system, organ, and tissue dysfunction or injury associated with high body temperature (generally >104°F [40°C]) at the time of injury from strenuous exercise and/or environmental heat exposure.38 Profound manifestations of exertional heat stroke are the result of a systemic inflammatory response that propagates the syndrome of multiorgan dysfunction. EHS occurs when the temperature regulation system is overwhelmed due to excessive endogenous heat production or inhibited heat loss and the body is no longer able to compensate and balance the heat load. Signs and symptoms include hyperthermia, tachycardia, hypotension, sweating, hyperventilation, altered mental status, vomiting, diarrhea, seizures, or coma.9 This multiorgan injury results from complex interplay between the cytotoxic effect of the heat and the inflammatory and coagulation responses of the subject, and again may lead to profound multiorgan dysfunction, and in some cases, death. Frequently encountered medical complications of EHS include acute respiratory distress syndrome, disseminated intravascular coagulation, shock, rhabdomyolysis, renal failure, cerebral edema, seizures, and hepatic dysfunction. The risk of mortality and morbidity increases the longer an athlete’s body is above 41°C but can be significantly reduced if the body temperature is lowered rapidly.10 The current evidence supports cold water immersion as the gold standard of cooling for an EHS victim.10 Although there is some debate as to what the optimal water temperature is for immersion, cold water immersion provides superior cooling rates compared with other cooling modalities such as ice-wet towels, ice packs over major arteries, or fanning.39 The most important factor in the treatment of EHS is the timeliness of rapid cooling, preferably performed on site by whatever means available. If rapid cooling can occur within 30 minutes from time of collapse (“the golden half hour”), the fatality rate approaches zero.11,12 Therefore, it is imperative that cooling start immediately and not be delayed for transport to the hospital: “cool first, transport second.”10

Compensation to Heat Stress and Thermotolerance

Although it has been hypothesized that previous heat illness predisposes to residual heat intolerance and an increased individual risk for recurrent heat illness, studies have not yielded a consistent conclusion.34 Heat intolerance can be present as early as 3 weeks postinjury and may persist as long as 5 years postepisode.35 This variability in heat intolerance may be due to inherent unique characteristics of the individual subject, which may include specific genetic mutations or myopathies (Table 1).35 Importantly, the lack of demonstrated recovery of heat tolerance may predispose an athlete returning to play prematurely to a second heat injury, potentially with significant consequence. Because of the serious, possibly life-threatening nature of a heat injury and the variable duration of

| Functional | Low fitness |
|------------|-------------|
|            | Poor acclimatization |
|            | Poor work efficiency |
|            | Decreased skin area to body mass ratio |
| Acquired   | Dysfunctional sweat glands |
|            | Dehydration |
|            | Infection |
|            | History of heat stroke |
|            | Medications/supplements |
| Congenital | Ectodermal dysplasia |

*Adapted from Epstein.18
heat intolerance, an objective measure of the ability to tolerate heat would be appealing before facilitating athletic RTP.

Return to Play

Healing from EHS and heat injury is clearly related to the duration of core temperature elevation above the critical level (approximately 104°F or 40°C). The longer a patient’s core temperature remains above this level, the greater the risk of severe morbidity and mortality and the longer the period needed for recovery. Knowledge of the precipitants of the EHS event (eg, infection, lack of acclimatization) as well as details of on-site and hospital treatment, if applicable, are key historical factors that help in guiding RTP.

Current research suggests that most individuals recover in a few weeks, especially those who were treated promptly and correctly. However, some athletes will experience long-term complications involving multiple organ systems, including the neurological system, as well as persistent heat intolerance. Definitive high-level evidence-based guidelines regarding RTP do not presently exist. The American College of Sports Medicine’s 2007 position stand recommended 1 possible RTP protocol (Table 2), which gradually progresses the athlete back to activity once symptoms and laboratory values have normalized. A

Any guidelines used to determine the approach and time frame for an athlete’s recovery must be modified based on the severity of illness. At a minimum, athletes should not return to any physical activity until they are symptom free and all laboratory values have returned to their baseline levels. A major challenge in RTP decision making is determining when exercise-heat tolerance deficit, neurological, or psychological impairments have corrected. Neuropsychological testing batteries similar to those used postconcussion to assess for impairment can be used. Neuropsychological exercise-heat tolerance testing may be useful in this setting. Additionally, batteries similar to those used postconcussion to assess for impairments have corrected. Neuropsychological testing may be performed to determine when the athlete is able to tolerate exercise in a cool environment and gradually increases the duration, intensity, and heat exposure over 2 weeks to demonstrate heat tolerance and initiate acclimatization.

Athletes who cannot resume vigorous activity over 4 weeks because of recurrent symptoms (eg, excessive fatigue) should be reevaluated. Laboratory exercise-heat tolerance testing may be useful in this setting. Once cleared for a return to activity, the athlete begins exercise in a cool environment and gradually increases the duration, intensity, and heat exposure over 2 weeks to demonstrate heat tolerance and initiate acclimatization.

The athlete may resume full competition once he or she is able to participate in full training in the heat for 2 to 4 weeks without adverse effects.

Table 2. RTP after EHS protocol

| • No exercise permitted for at least 7 days after release from medical care. |
| • Follow-up with the medical team approximately 1 week after release for physical examination and any necessary laboratory testing and diagnostic imaging based on the organs affected during the EHS episode. |
| • Once cleared for a return to activity, the athlete begins exercise in a cool environment and gradually increases the duration, intensity, and heat exposure over 2 weeks to demonstrate heat tolerance and initiate acclimatization. |
| • Athletes who cannot resume vigorous activity over 4 weeks because of recurrent symptoms (eg, excessive fatigue) should be reevaluated. Laboratory exercise-heat tolerance testing may be useful in this setting. |
| • The athlete may resume full competition once he or she is able to participate in full training in the heat for 2 to 4 weeks without adverse effects. |

EHS, exertional heat stroke; RTP, return to play.

Modified from Armstrong et al.

Heat Tolerance Testing

Currently, there is no standard that requires HTT prior to RTP and there is no universal protocol. The test must last at least 90 minutes and include heat exposure within the protocol. The Israeli Defense Forces (IDF) has been at the forefront of research and implementation of HTT prior to returning their soldiers to duty. The IDF protocol consists of walking for 2 hours at 5 km/h (3.1 miles/h) with a 2% incline in an environmental chamber set at 40°C (104°F) and 40% relative humidity. Subjects are asked to avoid medication, alcohol, tobacco, and caffeine prior to the test and are advised to be well rested and hydrated. Rectal temperature and heart rate are monitored during the test. Those whose core temperatures rise above 38.5°C and/or heart rate above 150 beats per minute are classified as heat intolerant. Tolerant subjects will demonstrate an initial rise in temperature and heart rate; however, these measures will plateau during the course of the test. Those who are intolerant will not achieve a plateau in these measures. Furthermore, a physiological strain index may be calculated, which is measured by weighted changes in core temperature and heart rate relative to those prior to the test.

Heat tolerance testing in RTP decision making after a heat injury is controversial. In most settings, HTT should only be considered for those athletes who are unable to return to vigorous activity after a period of recovery and acclimation (typically 4 weeks) or those who have had multiple episodes of EHS. If HTT is performed, it should occur approximately 1 month after the EHS event as long as clinical and laboratory indicators have normalized. The HTT is normal in about 90% of cases, and the athlete may RTP. If there is an abnormal response without apparent cause, it is then common to repeat the test in another 4 to 8 weeks (which is met with another
positive test less than 2% of the time) to refute or support the diagnosis of heat intolerance.41 EHS possibly results with heat intolerance of a short duration, intersubject variability may exist in recovery time of the thermoregulatory system, and the IDF HTT protocol is highly sensitive.54

EXERTIONAL RHABDOMYOLYSIS

Rhabdomyolysis can be defined as the breakdown of striated muscle fibers due to mechanical and metabolic insults that result in the release of muscle contents into circulation.39 ER can represent a pathological condition when muscle breakdown occurs after normal exercise and produces metabolic consequences that may include acute kidney injury, compartment syndrome, or even death.39 ER typically occurs in response to excessive, prolonged, or repetitive exercise; in addition, eccentric exercise appears to be more problematic.39

There can be a cascade of events that lead to ER, such as physical injury of muscle, accelerated muscle metabolism due to substances (eg, drugs, supplements) or underlying metabolic myopathies, hemoglobinopathies, and/or hyperthermia.46 These insults decrease intracellular adenosine triphosphate, which then leads to an increase in calcium in the sarcoplasm, which is coupled with a decrease in extracellular calcium and resultant hypocalcemia.39 The breakdown of muscle fibers releases the intracellular myocyte contents into the circulation: myoglobin, potassium, creatine kinase (CK), free radicals, and organic acids.39 These intramuscular components contribute directly to the disease process of ER.39 Myoglobin can overload the kidney resulting in acute kidney injury, while organic acids lead to metabolic acidosis, and potassium or other electrolyte abnormalities can predispose to cardiac arrhythmias. Finally, free radicals may contribute to tissue edema, increasing the risk of compartment syndrome.46 The severity of the disease is directly related to the amount of muscle breakdown that occurs.

In physiologic ER, the patient will develop an elevated CK but no other clinically significant signs or symptoms; while the athlete may have minimal muscle pain, the ER usually resolves without clinical sequelae.46 ER becomes clinically significant when there is severe muscle pain, swelling, or weakness as well as myoglobinuria and other metabolic consequences as mentioned. Risk factors for significant ER after excessive muscle exertion include dehydration, any medications or supplements that increase metabolism, alcohol, underlying myopathies, and excessive environmental heat exposure.37 Sickle cell trait has a unique relationship with ER and can result in a fulminant presentation.46 While physiologic ER presents with minimal muscle pain, significant ER patients will typically present with pain out of proportion with what would be expected and with dark (red, tea-, or cola-colored) urine. Although some would classify significant ER as any rhabdomyolysis with a serum CK level greater than 5 times the upper limit of normal, all athletes are different and there is not a true CK level, which indicates significant ER.46 Individual baseline CK levels may vary with ethnicity, sex, and level of physical fitness, and these factors must be taken into account when utilizing CK levels to diagnose ER or recovery from ER.35 The presence of myoglobinuria after exertion confirms pathologic ER.

The treatment for ER includes rest, aggressive hydration (usually with intravenous fluids), and monitoring for metabolic consequences (such as renal failure and electrolyte abnormalities) as well as the development of compartment syndrome. Because of the association between significant ER and hyperkalemia, an initial electrocardiogram is needed and cardiac monitoring utilized.39 Fulminant cases of ER complicated by significant acute kidney injury and related metabolic consequences may require dialysis. A second spike of CK during hospitalization may indicate occult compartment syndrome.39 For those who respond appropriately to hydration and rest without other complications from ER, activities can usually be resumed at a low level after resolution of symptoms.

Return to Play

Several issues must be addressed after an athlete recovers from ER before RTP decision making. First, is the athlete at risk for recurrence, and do they require further evaluation? Second, for those athletes not requiring further evaluation, when can they safely return to sport? And third, should any restrictions be placed on the athlete, and if so, for how long?

There is no clear evidence-based consensus on assessing those individuals at risk for recurrent events. The military demonstrated that long-term follow-up of Air Force recruits who had sustained an ER event in training had a very low risk of a subsequent event.7 The USUHS (Uniformed Services University of the Health Sciences) Consortium for Health and Military Performance (CHAMP), in conjunction with the Heller Institute of the Israeli Defense Force, compiled a consensus guideline to identify those at potential high risk who warrant a more detailed evaluation (Table 3).37 Low-risk cases of ER can begin a gradual RTP protocol (Table 4). High-risk cases (or those with a high risk of recurrence) may require further evaluation (Figure 1).

Once a patient has been identified as high risk, an exercise intolerance mutation profile, which screens for specific mutations in genes that encode for carnitine palmitoyltransferase II, myophosphorylase, and myoadenylate deaminase, is needed.35 It is less invasive than a muscle biopsy and may indicate metabolic myopathies.35 An alternative functional test to screen for metabolic disorders is the modified forearm ischemic exercise test.46 In select cases, however, a muscle biopsy may be required to further evaluate for myopathic etiologies.37

Because of the association between ER, EHS, and malignant hyperthermia (MH), it may be important to rule out heat intolerance or MH susceptibility as causative factors if clinically indicated. MH is an uncommon, autosomal, dominantly inherited disorder of calcium handling in skeletal muscle, mainly caused by mutations in the gene coding for the type 1 ryanodine receptor (RyR1), which functions to regulate the release of calcium from the sarcoplasmic reticulum.5 MH is typically asymptomatic unless unmasked by exposure to volatile inhaled anesthetics or succinylcholine.45 MH results in a hypercatabolic state associated with muscle breakdown
Heat intolerance can be assessed with the HTT while MH susceptibility can be done utilizing a caffeine-halothane contracture test (CHCT). Finally, genetic testing may evaluate for exercise intolerance mutations, which would predispose to more severe ER. The great majority of ER cases will not require advanced testing after risk stratification.

The high-risk workup may lead to a specific diagnosis or risk factor that then can be managed and mitigated. In high-risk cases where no diagnosis, risk factor, or mechanism is identified, RTP decisions should be made in open communication between the athlete and physician. Careful attention should be paid to known risk factors (e.g., supplements, infection, exercise, and environmental acclimatization).

### Table 3. Risk stratification for exertional rhabdomyolysis

| Suspicious for high-risk ER: |
|-------------------------------|
| a. Delayed recovery (>1 week) despite rest |
| b. Persistent elevation* of CK despite at least 2 weeks rest |
| c. ER complicated by acute renal injury |
| d. Personal or family history of myopathy, recurrent muscle cramps, or significant ER |
| e. Personal history of sickle cell trait (or family history of sickle cell disease) |
| f. Personal or family history of malignant hyperthermia or unexplained complications after general anesthesia |

| Low-risk athletes must have none of the high-risk conditions and at least 1 of the following: |
|-------------------------------|
| a. Rapid clinical recovery and CK/urine normalization after exercise restrictions |
| b. Sufficient fitness with a history of a very intense exercise bout preceding the ER |
| c. No personal or family history of myopathy, recurrent muscle cramps, or significant ER |
| d. Other cases (group or team related) of ER from same exercise sessions |
| e. Concomitant viral illness or infectious disease |
| f. Dietary supplements or medications that could contribute to ER |

CK, creatine kinase; ER, exertional rhabdomyolysis.

*Adapted from O’Connor et al.37

*greater than 5 times the upper limit of the normal lab range.

### Table 4. Return-to-play guidelines for exertional rhabdomyolysis—low risk

| Phase 1: |
|-------------------------------|
| • 72 hours rest and oral hydration |
| • Encourage a minimum of 8 hours of sleep nightly |
| • Remove from hot environment |

At 72 hours:

|-------------------------------|
| • If CK < 5× upper limit of normal AND urine has cleared, move to phase 2 |
| • If CK or urine is still abnormal at 72 hours, follow-up every 72 hours until cleared |
| • If CK or urine is still abnormal at 2 weeks, seek expert consultation |

| Phase 2: |
|-------------------------------|
| • Begin light activities at own pace and distance × 1 week |
| • If no symptoms, move to phase 3 |
| • If symptoms persist for 4 weeks, seek expert consultation |

| Phase 3: |
|-------------------------------|
| • Gradual return to sporting activities |
| • Follow-up only as needed |

CK, creatine kinase.

*Adapted from O’Connor et al.37
Fortunately, the majority of patients who develop ER will have none of the aforementioned disorders identified and may return gradually to normal activity after proper treatment and clinical recovery. Nevertheless, some cases may result from inherent predisposition.

**Exercise-Associated Sickle Cell Collapse**

Hemoglobinopathies are the most common genetic disease, affecting approximately 5% of the world's population. Approximately 300 million people worldwide and nearly 9% of African Americans in the United States (almost 3 million people) carry the sickle cell trait (SCT). SCT is diagnosed using the “sickledex” solubility test. However, the “sickledex” serves mainly as a first-line test; confirmation requires hemoglobin electrophoresis or another quantification method.

Sickle cell trait is largely benign but associated with hematuria, renal papillary necrosis, and splenic infarction. SCT is clearly associated with an increased relative risk of exercise-related sudden death in the military and athletes. In college athletes and military personnel with SCT, the risk of exercise-related death is about 40 times greater than those without SCT; however, the absolute risk of death is still very small.

The mechanism of collapse and exertional death with SCT remains controversial. Exertional sickling may occur with profound lactic acidosis, extreme muscle hypoxia, hyperthermia, and dehydration. An exertional surge in epinephrine may make SCT cells “sticky” and occlude the microcirculation in working muscles.

The sickle gene has 4 main haplotypes representing different geographic mutation origins: the Asian (India or Saudi Arabia), Benin (central West Africa), Senegal (West Africa above Niger River), and the Bantu (central and south central Africa). Bantu is the most severe, and the Senegal associated the mildest. Genetic variations may confer increased risk or perhaps protection against ECAST events.

Most cases of ECAST have occurred in preseason conditioning, on day 1 of summer camp, or after coming back from a vacation or injury. Attempts to run a given distance in a given time, compounded by a previous ER event or other musculoskeletal stressor, may “stack” subclinical sickling events, which may lower the threshold for fatal ECAST. The ability of SCT carriers to perform repeated short bouts of anaerobic predominant exercise with limited recovery time may be lower than non-SCT carriers.

The initial presentation of sickle collapse is often confused with heat cramping, heat exhaustion, or heat stroke. Unlike heat stroke, sickle collapse often occurs early in a workout in which an athlete’s core temperature would not have had time to rise. Furthermore, ECAST can be characterized as a “conscious collapse,” which may help differentiate this collapse from an acute cardiac event or EHS (Table 5). The most telling symptom of sickle collapse is increasing pain and weakness in muscles, especially the legs, buttocks, and low back. Early recognition of ECAST is critical for athlete survival, and emergency department physicians should be alerted to the possibility of explosive rhabdomyolysis. Treatment includes immediate hospital transfer for aggressive fluid and electrolyte management, as well as cardiac monitoring (Figure 2).
Table 5. General features of nontraumatic on-field collapse

| ECAST | EHS          | Acute Cardiac Event | Asthma/Respiratory Collapse |
|-------|--------------|---------------------|-----------------------------|
| Conscious, can talk | Altered mental status | Unconscious | Breathless, anxious |
| Slumps to ground | Bizarre behavior | Sudden collapse | Prior episodes |
| Temperature <103°F | Temperature >104°F | Often normothermic | Auscultate, poor air movement |
| May have cramping muscles | May have cramping muscles | Muscles normal | Excessive use of respiratory muscles |
| No seizure activity | May have seizure activity | May have seizure activity | May have seizure activity |
| Occurs early in practice | Occurs late in practice | No warning | Usually after high intensity |

ECAST, exertional collapse associated with sickle cell trait; EHS, exertional heat stroke.

*Adapted from Eichner.*

Figure 2. Recommendations for treating exertional collapse associated with sickle cell trait events. AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; ECAST, exertional collapse associated with sickle cell trait; EMS, emergency medical services; ER, emergency room; IV, intravenous; RTP, return to play.
The prevention of ECAST events centers on addressing known triggers: adherence to heat, hydration, and exercise acclimatization practices is recommended for those with SCT. Individuals with SCT as well as trainers and medical professionals should know and understand their SCT status. Currently, the National Collegiate Athletic Association (NCAA) and the Navy and Air Force mandate testing for SCT; professionals should know and understand their SCT status. Currently, the National Collegiate Athletic Association (NCAA) as well as trainers and medical professionals should know and understand their SCT status. Currently, the National Collegiate Athletic Association (NCAA) as well as trainers and medical professionals should know and understand their SCT status. Currently, the National Collegiate Athletic Association (NCAA) as well as the Navy and Air Force mandates testing for SCT; individual athletes can waive testing.

### Return to Play

There are no evidence-based RTP guidelines after an episode of ECAST. However, RTP should not be considered until the athlete is asymptomatic at rest and has normal end-organ function (Table 6). All RTP decisions with ECAST need to be individualized to the specific needs and risks of the athlete. Further, before any RTP decision making, a discussion with the athlete about risk mitigation strategies and risk of recurrence should occur (Table 7). Graded RTP programs with close supervision are recommended.

### CONCLUSION

While the prevalence of EHS, ER, and ECAST is low, these events still occur and challenge the sports medicine clinician with RTP decision making, challenged by a relative lack of evidence regarding natural course of disease, risk of recurrence, and guidance for return.

### REFERENCES

1. Akansheye I, Alsultan A, Solovieff N, et al. Fetal hemoglobin in sickle cell anemia. *Blood*. 2011;118:19-27.
2. Alpers JP, Jones LK Jr. Natural history of exertional rhabdomyolysis: a population-based study. *Muscle Nerve*. 2010;42:187-91.
3. Anzalone MK, Green VS, Buja M, Sanchez LA, Harrykisson BJ, Eichner ER. Sickle cell trait and fatal rhabdomyolysis in football training: a case study. *Med Sci Sports Exerc*. 2010;42:5-7.
4. Armstrong LE, Casa DJ, Millard-Stafford M, Moran DS, Pyne SW, Roberts WO. American College of Sports Medicine position stand. Exertional heat illnesses during training and competition. *Med Sci Sports Exerc*. 2007;39:556-572.
5. Best TM, Brøllin RG. Return to play: the sideline dilemma. *Clin J Sport Med*. 2005;15:403-404.
6. Binkley HM, Beckett DJ, Casa DM, Kleiner DM, Plummer PE. National Athletic Trainers’ Association position statement: exertional heat illnesses. *J Athl Train*. 2002;37:329-343.
7. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med*. 2002;346:1978-1988.
8. Brukner P. Return to play—a personal perspective. *Clin J Sport Med*. 2005;15:459-464.
9. Capaccioni JF, Sambouahin 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 α-1 subunit gene, and calsequestrin-1 gene polymorphisms. *Anesthesiology*. 2010;112:239-244.
10. Casa DJ, Armstrong LE. Heatstroke: a medical emergency. In: Armstrong LE, ed. *Exertional Heat Illnesses*. Champaign, IL: Human Kinetics; 2003:29-36.
11. Casa DJ, Armstrong LE, Kenny GP, O’Connor FG, Huggins RA. Exertional heat stroke: new concepts regarding causes and care. *Curr Sports Med Rep*. 2012;11:115-123.
12. Casa DJ, McDermott BP, Lee EC, Yeargin SW, Armstrong LE, Maresch CM. Cold water immersion: the gold standard for exertional heatstroke treatment. *Exerc Sport Sci Rev*. 2017;35:141-149.
13. Connes P, Sara F, Hardy-Dessources MD, et al. Effects of short supramaximal exercise on hemorheology in sickle cell trait carriers. *Eur J Appl Physiol*. 2006;97:145-150.
14. Deuster PA, Contreras-Seveso CL, O'Connor FG, et al. Genetic polymorphisms associated with exertional rhabdomyolysis. Eur J Appl Physiol. 2015;115:1997-2004.

15. Eichner ER. Sickle cell considerations in athletes. Clin Sports Med. 2011;30:537-549.

16. Eichner ER. Sickle cell trait in sports. Curr Sports Med Rep. 2010;9:347-351.

17. Eichner ER. Sports medicine points and pitfalls—sickle cell trait and athletes: three clinical concerns. Curr Sports Med Rep. 2007;6:134-135.

18. Epstein Y. Heat intolerance: predisposing factor or residual injury? Med Sci Sports Exerc. 1990;22:29-35.

19. Epstein Y, Heled Y. Back to play of athletes after exertional heat stroke. Curr Sports Med Rep. 2012;11:336-340.

20. Grant AM, Parker CS, Jordan LB, et al. Public health implications of sickle cell trait: a report of the CDC meeting. Am J Prev Med. 2011;41(6 suppl 4):S435-S439.

21. Harmon KG, Drezner JA, Klossner D, Asif IM. Sickle cell trait associated with exertional death in physical training. Am J Prev Med. 2011;41(6 suppl 4):S435-S439.

22. Heled Y, Bloom MS, Wu TJ, Stephens Q, Deuster PA. CK-MM and ACE genotypes and physiological prediction of the creatine kinase receptor to exercise. J Appl Physiol (1985). 2007;103:504-510.

23. Herring SA, Kibler WB, Putukian M. The team physician and the return-to-play decision: a consensus statement—2012 update. Med Sci Sports Exerc. 2012;44:2446-2448.

24. 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 suppl 4):S406-412.

25. 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;317:781-787.

26. Kenney K, Landau ME, Gonzalez RS, Hundertmark J, O'Brien K, Campbell WW. Genetic polymorphisms for the sports medicine staff. Clin Sports Med. 2011;30:135-149.

27. Monchalin G, Serpero LD, Connes P, et al. Effects of progressive and maximal exercise on plasma levels of adhesion molecules in athletes with sickle cell trait with or without α-thalassemia. J Appl Physiol (1985). 2007;102:169-175.

28. Moran DS, Erlich T, Epstein Y. The heat tolerance test: an efficient screening tool for evaluating susceptibility to the heat. J Sport Rehabil. 2007;16:215-221.

29. Moran DS, Heled Y, Still L, Lau A, Shapiro Y. Assessment of heat tolerance for post exertional heat-stroke individuals. Med Sci Monit. 2004;10:CR252-CR257.

30. Muldoon S, Deuster P, Voelkel M, Capacciojone J, Burger R. Exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia: is there a link? Curr Sports Med Rep. 2008;7:74-80.

31. Mehta AC, Baker RN. Persistent neurological deficits in heat stroke. Neurology. 1970;20:536-540.

32. Monchalin G, Serpero LD, Connes P, et al. Effects of progressive and maximal exercise on plasma levels of adhesion molecules in athletes with sickle cell trait with or without α-thalassemia. J Appl Physiol (1985). 2007;102:169-175.

33. Moran DS, Erlich T, Epstein Y. The heat tolerance test: an efficient screening tool for evaluating susceptibility to the heat. J Sport Rehabil. 2007;16:215-221.

34. Moran DS, Heled Y, Still L, Lau A, Shapiro Y. Assessment of heat tolerance for post exertional heat-stroke individuals. Med Sci Monit. 2004;10:CR252-CR257.

35. Muldoon S, Deuster P, Voelkel M, Capacciojone J, Burger R. Exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia: is there a link? Curr Sports Med Rep. 2008;7:74-80.

36. O'Connor FG, Bergeron MF, Cantrell J, et al. ACSM and CHAMP summit on sickle cell trait: mitigating risks for warfighters and athletes. Med Sci Sports Exerc. 2012;44:2495-2496.

37. O'Connor FG, Brenman FH Jr, Campbell W, Heled Y, Deuster P. Return to physical activity after exertional rhabdomyolysis. Curr Sports Med Rep. 2008;7:328-331.

38. O'Connor FG, Casa DJ, Bergeron MF, et al. American College of Sports Medicine roundtable on exertional heat stroke—return to duty/return to play: conference proceedings. Curr Sports Med Rep. 2010;9:314-321.

39. O'Connor FG, Deuster PA. Rhabdomyolysis. In: Goldman L, Schafer A, eds. Goldman's Cecil Medicine. 24th ed. Philadelphia, PA: Saunders Elsevier; 2012:700-705.

40. Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia: a molecular disease. Science. 1949;110:543-548.

41. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle gene and geographical confirmation of the malaria hypothesis. Nat Commun. 2010;1:104.

42. Powars DR, Meiselman HJ, Fisher TC, Hill A, Johnson C. Beta-S gene cluster haplotypes modulate hematologic and hemorheologic expression in sickle cell anemia. Use in predicting clinical severity. Am J Pediatr Hematol Oncol. 1994;16:55-61.

43. Pratte-Rhodes LD, Eichner ER, Beutler A, Adams WB, O'Connor FG. Exercise collapse associated with sickle cell trait (ECAST): case report and literature review. Curr Sports Med Rep. 2015;14:110-116.

44. Shapiro Y, Magazanik A, Udassin R, Ben-Barch G, Shvartz E, Shoenfeld Y. Heat intolerance in former heat stroke patients. Ann Intern Med. 1979;90:913-916.

45. Sheltmadine BD, Bahrnsperger A, Wilson BL, Bowden RG. Rhabdomyolysis and acute renal failure in a sickle cell athlete: case study. Clin J Sport Med. 2013;23:255-257.

46. Szczepanik ME, Heled Y, Capacciojone C, Campbell W, Deuster P, O'Connor FG. Exertional rhabdomyolysis: identification and evaluation of the athlete at risk for recurrence. Curr Sports Med Rep. 2014;13:115-119.

47. Tarnopolosky M, Stevens L, MacDonald JR, et al. Diagnostic utility of a modified forearm ischemic exercise test and technical issues relevant to exercise testing. Muscle Nerve. 2005;27:559-565.

48. Tsaras G, Owusu-Ansah A, Bouteng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. Am J Med. 2009;122:507-512.