Sickle Cell Trait in Warriors and Athletes: What We Know, What We Don’t Know, and Where We Go From Here!

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Objectives

- **Review** the relevant background of sickle cell trait in warriors and athletes (WA).
- **State** what is currently **known** about SCT in WA.
- **State** what is currently **unknown** about SCT in WA.
- **Discuss** recommendations for where we go from here.
Case 1

- 26 y/o male AA warrior, SCT positive, completes his PT test (push-ups, sit-ups, and 1.5 mile run).
- This is his fourth test; 11:30 run consistent with three prior efforts.
- Ambient temperature of 50 °F.
- Complains of marked dizziness on cool down lap.
Case 2

- 30 y/o male AA warrior referred to lab to further evaluate episode of exertional rhabdomyolysis.
- Extremely fit prior soccer player with no history of prior cramping.
- Engages in Cross Fit workout with emphasis on squats.
- Awakes at night in severe back pain and can’t walk.
Case 3

- A 20 y/o AA male midshipmen was unable to complete his fitness assessment due to severe leg pain and weakness 70 yards 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 transported to the medical clinic; his only complaint was ongoing severe thigh and hamstring pain that made it difficult to walk.
Case 4

- 34 y/o Marine was participating in a CFT like field competition event.
- He reports during his first event, a 440 m sprint, he experienced tightening and severe (10 / 10) pain approximately ¾ of way through the run.
- It was all he could do to push himself across the finish whereupon he collapsed and was unable to walk on his own.
The National Collegiate Athletic Association (NCAA) adopted a policy requiring Division I institutions to perform sickle cell trait testing for all incoming student athletes.

Policy was partly in response to legal settlement with Dale Lloyd Case.

But then….
Policy **Opposes Mandatory SCT Screening** for Athletic Participation

– Recommends universal training interventions and additional research

Believes NCAA Division I policy, as currently written and implemented, **has potential to harm student athletes and larger community of individuals with SCT.**

Not Everyone is Thrilled with Screening!

What is a Sports Medicine Physician to Think?
Request from US Army TRADOC

- Two soldier deaths during basic training associated with SCT
- December 2010
- General Martin Dempsey

...
ACSM DoD Consensus Conference on SCT

Dr. John Kark

Dr. Randy Eichner

Dr. Kwaku Ohene-Frempong

Dr. Alexis Thompson
What is Currently Known about Athletes with SCT?
SCT is Common, and Generally Benign!

- Approximately 3 million people in the US and 300 million in the world have SCT.
- Presence of SCT appears to be protective against severe falciparum malaria.
- Prevalence in US:
  - Blacks: 1/14,
  - Hispanic/Latino: 1/183,
  - Whites: 1/625
- 4/10 West Africans have SCT!
Hemoglobins (Hb) are tetramers of two pairs of two types of globins, each attached to a heme subunit.

- Alpha-globin gene family is located on short arm of chromosome 16
- Beta-globin gene family is located on short arm of chromosome 11.
- Each red blood cell has ~ 280 million Hb molecules.
- More than 1,100 Hb variants occur and result from a wide variety of genetic events – mostly base-pair mutations in globin genes.
SCT Athletes: Excel in Sports at All Levels

- SCT carriers on Ivory Coast established 32/33 national records on running courses of 400 meters or shorter
  - Suggests greater ability of SCT carriers to perform in short and intense running events than in endurance courses.
- SCT athletes successfully competed in Olympic games in Mexico City….and the NFL.

SCT is Associated with Sudden Death

“Current cumulative evidence is convincing for associations with hematuria, renal papillary necrosis, hyposthenuria, splenic infarction, exertional rhabdomyolysis, and exercise-related sudden death.”

*Other Causes of Death:

- 22 suicides
- 12 lightening strikes
- 13 drownings
- 9 aneurysms
- 8 SCT related rhabdo (<1% of Cohort)
- 2 epileptic seizures, and
- 4 miscellaneous

RESULTS:

- During the 5-year period, there were 273 deaths and a total of 1,969,663 athlete participation-years.
- Of these 273 deaths, 145 (53%) were due to accidents or unintentional injury, 45 (16%) from cardiac arrest, 25 (9%) suicides, and 18 (6%) homicides.
- Motor vehicle accidents accounted for 100 accidents (69%).

CONCLUSIONS:

- Motor vehicle accidents are the most common cause of sudden death in athletes across NCAA divisions, gender, race, and sport.

Sickle Cell Trait and Sudden Death

**Military:**
- Study of >450,000 military recruits (1977-1981)
- SST+ 30X risk sudden death: \{RR 30 (11 – 84)\}


**Civilian**
- NCAA SCT deaths 2004 to 2008 = 5.
- SST +15X risk of sudden death.
- D1 football players alone: SCT African Americans (AA) have a RR of 1:805; or 37x risk relative to those without SCT.

“Excess” sudden deaths in SCT due to Exertional Heat Illness (EHI)
- + Sudden Cardiac Death
- + Acute, Fulminant Renal Failure

Major Predictor of heat exposure in previous 48 Hours was (WBGT > 75F)
- SCT + Sudden Death: OR: 17
- EHI (SCT -) OR: 16
- Idiopathic Sudden Death – OR: 9
- Sudden Cardiac Death – OR: 5
Mitigating Heat Appears to Make a Difference!

<table>
<thead>
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<th>1.8 Million recruits</th>
<th>1.0 Million recruits</th>
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<td>37,000 SCT +</td>
<td>26,000 SCT +</td>
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Fundamental changes in training regimen (all recruits)

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<th>Predict Deaths</th>
<th>Actual Deaths</th>
<th>Lives Saved</th>
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<td>13</td>
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<tr>
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No changes in training regimen (all recruits)

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<th>Predict Deaths</th>
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<tr>
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<td>15</td>
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Heat is NOT the Trigger for Sickling…it’s Intensity!

- EHI Not a Factor in NCAA Deaths
  - None of 10 NCAA football deaths
  - Often NCAA collapse happens early in workout

- EHI Not Proven in Army Deaths
  - Most Army deaths Core Temp < 102° F
  - Many others no Core Temp taken

“Heat is no more a trigger for exertional sickling than is altitude, asthma, heedless valor, or a reckless coach”

Hemorheology and SCT: Main Findings

- **At rest**, SCT carriers usually have **marked increased blood viscosity**, slightly increased RBC disaggregation threshold and increased plasma adhesion molecule VCAM-1 concentration.

- Exercise results in a greater decrease in RBC deformability in SCT carriers than controls during late recovery, but **adequate hydration can normalize hemorheological abnormalities of SCT carriers**.

- **Exercise activates leucocytes** and platelets more in SCT carriers than controls.

- Very few coagulation differences have been noted between SCT carriers and controls.

Hemorheology and SCT: Main Findings

- Resting blood viscosity was greater in the SCT carriers than in the Control group.
- The change in blood viscosity occurring in SCT carriers during soccer games was dependent on the experimental condition: (1) in dehydration condition, blood viscosity rose over baseline; (2) in hydration condition, blood viscosity decreased below resting level reaching Control values.
- This study demonstrated that ad libitum hydration in exercising SCT carriers normalizes the blood hyperviscosity.

Sickle cell solubility test is a widely used screening method for sickle cell anemia; mandated by NCAA in 2010.

Sickle cell solubility test relies on the relative insolubility of Hb S in concentrated buffers compared to Hb A and other Hb variants.

Hb S precipitates to cause a cloudy solution.

Sensitivity of test is 98.5 - 98.9%.

Facts: The Sickle Cell Solubility Test

- Assuming 100% effective intervention, 144,181 athletes would need to be screened to prevent one death.” Tarini

- Evaluating Test Parameters of Solubility Test:
  - Assuming 99% sensitivity and 100% specificity.

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<thead>
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<th>SCT Carrier</th>
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<tr>
<td>Positive</td>
<td>2125</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>22*</td>
<td>142,034</td>
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<tr>
<td></td>
<td>2,147</td>
<td>142,034</td>
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Whereas screening 144,181 athletes may prevent one death… 22 athletes will be misidentified as SCT negative.

Case 1

- Warrior is evaluated immediately by medical staff.
- No complaints of cramping or weak legs.
- With hydration recovers quickly and asks to return to barracks.
- Collapses after walking 30 yards.
- EMT transport.
Case 2

- Pt is seen in ER and diagnosed with exertional rhabdomyolysis with paraspinal myonecrosis.
- Requires emergent operation with a fasciotomy.
- Laboratory testing to include exercise intolerance panel and myoglobinuria panel are performed.
Case 3

- A Junior at the US Naval Academy, he had completed numerous vigorous military training evolutions with no apparent problems.
- He also trained regularly for semi-annual fitness assessments, and regularly played intramural soccer.
- He had failed multiple prior fitness runs, although he passed each run on make-up testing. Over the prior 2 years, he had complained of “muscle cramps” in his legs and had noted increasingly longer recovery times.
Case 4

- Prior to this event patient reports that he has never had any exertional difficulties.
- He joined the Marine Corps 8 years ago and went through rigors of boot camp and subsequent year of physical training and fitness tests without incident.
- He played soccer in high school and is accustomed to running, which is why he was chosen to be the 440 sprinter for his field competition team.
- He denies any illness or ill symptoms prior to this incident. He is on no medication and denies any supplement use.
What is Currently Unknown about SCT in Athletes?
What is the Mechanism of Sudden Death?

This is a Hypothesis!!

Why is this Entity Not Commonly Seen in SCD Population?

- **Principal Complications:**
  - **Painful Vasocclusive Crisis**
    - severe pain due to infarctions in the bones, joints, lungs, liver, kidney, spleen, eye, or central nervous system, an acute condition seen with sickle cell anemia.
  - **Splenic Sequestration Crisis**
  - **Aplastic Crisis**
  - **Hemolytic Crisis**
  - Infrequent observations in patients with SCD of reversible muscle injury.

Is SCT Death the “Tip of the Iceberg”? 

- “For Every Fatal Collapse, 3-5 Nonfatal Events”
  - Lumbar paraspinal myonecrosis
  - Non-fatal rhabdomyolysis

- Study of 5K SCT + and 236K SCT –
  - No Difference in Rates of Reversible muscle symptoms

“... since sickling is known to occur postmortem, it remains controversial as to whether the pathogenesis of these exercise related deaths involves microvascular obstruction by sickled erythrocytes.”

“SCT has to be reconsidered as a single-hemoglobin gene mutation.

This means that subjects with SCT are similar for this gene, but may be different for all other hemoglobin genes.

…subjects with SCT may also be different with regard to all their remaining genes.”

BLUF: Not all SCT Athletes are the Same!

Case 1

- Warrior succumbs.
- NI potassium; nl CK.
- Autopsy with evidence of borderline heart, and massive sickling.
- Death labeled as complication of SCT.
- Warrior was screened and identified as higher risk.
Case 2

- Warrior is diagnosed with Phosphofructokinase deficiency.
- Nutrition consultation.
Case 3

- Pt was hospitalized at Bethesda National Naval Medical Center.
- On hospital day 2, disseminated intravascular coagulation (DIC) emerged.
- As the patient became more obtunded, compartment syndromes developed; he underwent multicompartment fasciotomies of thighs and lower legs.
- Acidosis and hyperkalemia remained problematic despite renal dialysis. He was kept sedated on ventilator following surgery.
- With a CK peak of 3 million IU/L, hyperbaric oxygen therapy was begun to try to salvage non-necrotic muscle.
- On hospital day 23, no brainstem reflexes could be elicited.
Case 4

- Pt with recalcitrant leg pain, was transferred to a local treatment facility.
- Peak CK of 182,000 on day three of hospitalization.
- Discharged and presently under evaluation for return to duty.
Given What is Known and Unknown about SCT in Athletes...

Where do we go From Here?
We Need an SCT Registry

- Several centers presently exist to describe sudden death in young athletes.
- A Center devoted to SCT research involving athletes would be “one” step forward.

Dr. Frederick Mueller

National Center for Catastrophic Sport Injury Research
We Need Common Terminology!

- After considerable debate, the collective group elected that clinical syndromes observed in SCT WA populations be identified as “ECAST”.
- “Exercise Collapse Associated with Sickle Cell Trait”.
Clinical Research We Need to Lead!

- Assess **efficacy of current risk mitigation strategies** (i.e. hydration, heat, exercise intensity) used in collegiate athletics and/or the military.
- **Assess risks and benefits of NCAA’s SCT screening program**, as it pertains to outcome, program cost-effectiveness, and potential discriminatory implications.
- Conduct prospective studies on large cohorts of collegiate athletes and military basic training recruits to compile **careful protocol-driven records**.
- Conduct DNA testing on cases to clearly identify: ethnicity; **full genotype of Hb S heterozygotes; other genetic abnormalities**.
In the Meantime…

- Target screening of high-risk groups;
- Introduce aggressive educational intervention for athletes with SCT and those who supervise them;
- Allow appropriate time and access for hydration of athletes;
- Acclimate gradually to novel activity and heat;
- Modify activity in heat and at altitude;
- Implement appropriate strength and conditioning programs developed by qualified strength and conditioning coaches;

In the Meantime…

- Prohibit punitive exercise and conditioning sessions;
- Recognize athletes who are struggling early on, so they can immediately be allowed to rest and not pushed past their physiologic limit;
- Develop adequate emergency plans for all individuals responsible for athletes during training and conditioning.

In general, student-athletes with sickle cell trait should:

- Set their own pace.
- Engage in a slow and gradual preseason conditioning regimen to be prepared for sports-specific performance testing and the rigors of competitive intercollegiate athletics.
- Build up slowly while training (e.g., paced progressions).
- Use adequate rest and recovery between repetitions, especially during “gassers” and intense station or “mat” drills.
- Not be urged to perform all-out exertion of any kind beyond two to three minutes without a breather.
- Be excused from performance tests such as serial sprints or timed mile runs, especially if these are not normal sport activities.
- Stop activity immediately upon struggling or experiencing symptoms such as muscle pain, abnormal weakness, undue fatigue or breathlessness.
- Stay well hydrated at all times, especially in hot and humid conditions.
- Maintain proper asthma management.
- Refrain from extreme exercise during acute illness, if feeling ill, or while experiencing a fever.
- Access supplemental oxygen at altitude as needed.
- Seek prompt medical care when experiencing unusual distress.
Q: Can an individual with sickle cell trait participate in athletics/exercise?

- **A:** Sickle cell trait should not be an impediment for participation in athletics or physical exercise. Maintaining good hydration and understanding how to avoid injuries can make exercise safer for ALL individuals, including those with sickle cell trait.
What precautions should an individual with sickle cell trait take when participating in sports or exercise?

- **A:** Individuals with sickle cell trait should consider the same precautions that can prevent injuries and exercise-related illnesses as people who do not have sickle cell trait. These include being mindful of heat and humidity, drinking adequate fluids, taking rest breaks as needed, and not exceeding their current level of fitness.
My Final Thoughts…

- We have two obligations as physicians:
  - *Primum non nocere* or “Do No harm”
  - To Never be afraid to Question…in particular when there may be data inconsistencies!