Sickle cell trait and fatal exertional heat illness: implications for exercise-related death of young adults.

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Studies in Collaboration

with

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# Sickle cell trait and fatal exertional heat illness: implications for exercise-related death of young adults

Objectives

1) Analyze specific mortality rates to characterize sickle cell trait as a risk factor for exercise-related death.

2) Examine factors important to prevent EHI among all recruits.

3) Interpret results of a controlled prospective intervention to prevent EHI on exercise-related mortality for recruits.

4) Provide practical recommendations to reduce exercise-related death in young adults with or without sickle cell trait.
Formation of deoxy-Hemoglobin S Polymers

- Deoxy Hb S polymer forms more rapidly with hypoxemia, as Hb concentration increases - $[\text{Hb S}]^{35}$, acidosis, high temperature, high BPG
- Relevant to high risk for specific sites: arterioles in the renal papillae, vessels of the spleen
- Exercise produces hypoxia, dehydration, acidosis, hyperthermia, and increasing BPG
Sickle Cell Trait

- Hb AS genotype. Hb S <50% (SS, SC, Sbeta-thal : Hb S >50%)
- Median Hb S is 42%, (33%, 26% for Hb AS with 3 or 2 alpha globin genes)
- Normal CBC with no anemia, hemolysis undetectable
- Microscopic sickling significant in the loops of Henle of the renal medulla, occasionally in the spleen, and in the drainage of vitreous humor post-trauma
- Reversible sickling is detectable and increases during exercise.
- Large population studies show normal survival and slight increased admission for hematuria
Clinical Complications Proven to Be Associated with Sickle Cell Trait

- Age-related loss of maximal urinary concentration, episodic hematuria, mild increase in UTI of pregnancy
- Altitude & exercise related splenic infarction
- Traumatic hyphema
- Renal medullary carcinoma
- ? reports of increased VTE: Heller ’73, Austin ‘07
- Unexpected exercise-related death in recruits and young athletes
Exertional Heat Illness (EHI)

- Muscle metabolism: 20% work and 80% heat.
- Heat is removed by water with sweating (conduction, convection, evaporation) with water & electrolyte loss.
- Blood flow to muscle and skin increases while visceral flow decreases. Shock & gut and kidney ischemia may result.
- Muscle & liver necrosis: like tumor-lysis syndrome.
- Acute renal failure due to myoglobin-induced ATN, hyperuricemia, hypo-perfusion.
- Hyperthermia causes non-focal encephalopathy.
- Tissue injury induces inflammation and DIC.
Major Fatal Syndromes of EHI

- **Rhabdomyolysis.** Acute necrosis of muscle (or liver). Similar to Tumor lysis syndrome. Myoglobin and skeletal CK are markers. Initial Rx is aggressive alkaline hydration. Treat electrolyte imbalance, ARF, occasional hypoglycemia. Hyper-K+/hypo-K+, acidosis common.

- **Heat stroke.** Non-focal encephalopathy w hyperthermia, rapid response to cooling and hydration. Shock, Seizures, coma.

- **Acute renal failure.** Provoked by early salt intake. Hydration w alkaline saline, prevent myoglobin related ATN, monitor and correct metabolic problems.
THE SPECTRUM OF EXERTIONAL HEAT ILLNESS

- Hyperthermia
- Dehydration
- Nephropathy
- Cell Lysis
- Encephalopathy

Heat Exhaustion
- Heat Injury
  - Renal Failure
  - Rhabdo-myolysis
  - Heat Stroke

Shock

Moderate → Severe
Ideal Features for Study of Unexpected Exercise-Related Deaths in Young Adults

Enumerated described population of at least a million exercising people.

All deaths studied by autopsy w/o restriction to sudden death (requiring life-support w/in one hour).

All deaths with adequate data: PMH, eyewitness accounts, clinical records, full autopsy, toxicology, Review by CV, Forensic subspecialists, Training conduct.

Body temperature and lab tests for rhabdomyolysis/ARF. (5% of sudden death).
Hemoglobin S and Rates of Exercise-Related Death Unexplained by Preexisting Disease

<table>
<thead>
<tr>
<th></th>
<th>with Hb AS</th>
<th>without Hb S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Recruits*</td>
<td>37,300</td>
<td>429,000</td>
</tr>
<tr>
<td>Cases</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Rate/10^5 p*yrs</td>
<td>227</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Relative Risk  =  30

(95% CI = 11 to 84)  (p-value <10^{-6})

# Sickle Cell Trait as a Risk Factor for Exercise Related Death among Recruits

<table>
<thead>
<tr>
<th></th>
<th>Hb AS Rate per 10^5</th>
<th>w/o Hb S Rate per 10^5</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Deaths</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Races</td>
<td>244</td>
<td>8.8</td>
<td>28</td>
</tr>
<tr>
<td><strong>Unexplained</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths among Blacks</td>
<td>227</td>
<td>7.6</td>
<td>30</td>
</tr>
<tr>
<td>Blacks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Exercise Related Death in Civilian* versus Recruit Populations


<table>
<thead>
<tr>
<th></th>
<th>Rate per 100,000/yr</th>
<th>Rate per 100,000/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(white males, 30-64 yrs)</td>
<td>13.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Recruit Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AA, 17-30 yrs)</td>
<td>8.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Recruit Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AS, 17-30 yrs)</td>
<td>244</td>
<td>2.4</td>
</tr>
</tbody>
</table>
## Exercise-Related Deaths of Recruits

<table>
<thead>
<tr>
<th>Deaths unexplained by pre-existing disease</th>
<th>Hb AS</th>
<th>w/o Hb S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Deaths unexplained by pre-existing disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rhabdomyolysis w/o heat stroke</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>• Heat stroke w/ rhabdomyolysis</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>• Heat stroke alone</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>• Idiopathic sudden death</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Deaths attributed to pre-existing disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sudden cardiac</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>• Non-cardiac</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Exercise-Related Deaths in Recruit Entry Training for 1977-1981

1. 55% of cases were fatal EHI: mainly with non-sudden death in renal failure

2. 45% of cases were idiopathic sudden death (IDS) in cardio-pulmonary arrest.

3. There was no difference in clinical picture by hemoglobin phenotype.

4. Analysis of 35 cases of ERD with Hb AS:
   17 sudden deaths: 9 Rhab’ 1 HS. 6 ISD.
   18 non-sudden deaths: 13 Rhab’ & 4 HS + Rhbd.
Common Characteristics of the Exercise-related Idiopathic Sudden Deaths

Most deaths were related to 1-3 mile runs (sustained high metabolic activity).

Most were during summer months early in the morning at a WBGT heat index <75°F.

There was seldom significant hot weather by conventional standards (≥85°F), although some had exposures from 75 to < 85°F during running.

Perhaps prior-day and same-day heat exposures contribute to unrecognized fatal EHI. Perhaps some present as idiopathic sudden death.
Wet-Bulb Globe Temperature Index

The WBGT Index takes into account air temperature, humidity, radiant heat, and air movement.

\[
WBGT \text{ Index} = 0.7(W) + 0.2(G) + 0.1(D)
\]

- \(W\) = Aspirated Wet-Bulb Temperature
- \(G\) = Matte Black Globe Temperature
- \(D\) = Dry-Bulb Temperature
Epidemiology of Non-fatal EHI: Parris Island MCD 1979-1995

I was the PI for clinical observational studies of this population to improve Dx, Rx, Prevention of EHI.

Parris Island was the only recruit center with consistent detailed surveillance records.

The epidemiology of EHI was studied by review of all cases from 1979-1995 for 300,000 recruits.

All cases were reviewed with clinicians on site during 1986-1992. There were 3,000 out-patient and 300 hospitalized cases of EHI in our data-base.
## Rates of EHI w/ or w/o Hb AS

**Among Parris Island Recruits 1982-1991**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Observed</th>
<th>Population</th>
<th>Rate/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild &amp; Hb AS</td>
<td>32</td>
<td>5010</td>
<td>6.4</td>
</tr>
<tr>
<td>Mild &amp; No Hb S</td>
<td>1609</td>
<td>262728</td>
<td>6.1</td>
</tr>
<tr>
<td>Hospitalized &amp; Hb AS</td>
<td>0</td>
<td>5010</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>Hospitalized &amp; No Hb S</td>
<td>225</td>
<td>262728</td>
<td>0.86</td>
</tr>
</tbody>
</table>
Comparison of Rates of Moderate EHI with or w/o Hb AS

• Recruits with sickle cell trait had the same rates of moderate EHI (out-patient or in-patient) as recruits without sickle cell trait. In-patients often had periods of high risk in the ER but seldom after admission.

• Study Limitation: These recruits received excellent early care by an intervention capable of preventing severe EHI. Few suffered life-threatening rhabdomyolysis.

• These results favor the view that sickle cell trait increases mortality of severe EHI rather than initiating development of non-life threatening injury from EHI.
HYPOTHESIS

Exertional heat illness (EHI) is a frequent risk factor for exercise-related sudden death

- **POPULATION:** 269,000 Marine Corps recruits at Parris Island, SC, 1979-1990.
- **COLLECT:** All EHI and all threatened or actual sudden deaths during training. *(Too small for mortality as the end-point)*
- **COMPARE:** Rates of fatal or serious cardiovascular events in those with or without EHI and with or without Hb AS.
Spectrum of Clinical Presentations

• Sought all types of EHI but 10/11 serious cases had exertional heat stroke.
• Sought cases of distributive shock, life-threatening arrhythmias, and ischemia/infarction. Found shock or cardiac arrest/ including 2 w arrhythmia.
• No recruits with serious events had sickle cell trait (population to small)
Comparison of EHI and Structural Cardiac Lesions for risk of Life-Threatening Events

- There were 11 adverse CV events.
- 8 had EHI: 6 of these had Heat Stroke followed by shock. 2 presented as sudden cardiac arrest in asystole unresponsive to ACLS. One had heat stroke and one had Rhabdo’ with coronary anomalies.
- There were two other deaths from cardiac disease (coronary anomalies and myocarditis).
- There was one idiopathic sudden death while swimming.
- EHI contributed to 8/11 cases and silent heart disease to 3/11 cases.
- These data support the hypothesis that preventable EHI is an important component of exercise-related sudden death among healthy young adults.
# Exertional Heat Illness as a Risk Factor for Threatened or Actual Sudden Death

<table>
<thead>
<tr>
<th></th>
<th>Exertional Heat Stroke</th>
<th>Without Heat Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td>7 (2d)</td>
<td>4* (4d)</td>
</tr>
<tr>
<td>Population at risk</td>
<td>137</td>
<td>267,000</td>
</tr>
<tr>
<td>Case Rate</td>
<td>5.1%</td>
<td>0.0015%</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>3,400</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>
1982-91 Recruit Heat Illness Cases by Gender and Time of Day
Recruit Heat Illness by WBGT Category at Time of Illness, 7-9 am Cases

- Case Rates
- Case Counts

WBGT Category (°F)
- <60
- 60-<65
- 65-<70
- 70-<75
- 75-<80
- 80-<85
- 85-<88
- 88-<90
- 90+

Cases per 100,000 person-hours
- 0
- 50
- 100
- 150
- 200
- 250
- 300
- 350
- 400
- 450

Number of Cases
- 0
- 50
- 100
- 150
- 200
- 250
- 300
- 350
- 400
- 450
Recruit Heat Illness by WBGT Category of Prior Day Maximum, 7-9 am Cases

Case Rates
Case Counts

WBGT Category (°F)

Number of Cases

Cases per 100,000 person-days
Association of WBGT level with EHI Cases

- About one-third occurred with immediate exposure to WBGT at least 75°F.
- About 50% were related to prior day WBGT at least 75°F.
- The two temperatures were not closely related.
- If one wished to reduce events, activity restrictions could start at lower WBGT levels.
Types of Exercise Related Recruit Deaths
(94 military recruit deaths, 1977-90)

- **HS & Rhabdo (EHI)**: 10 w/ SCT, 15 w/o SCT
- **Idiopathic (ISD)**: 7 w/ SCT, 15 w/o SCT
- **Expl Cardiac (SCD)**: 2 w/ SCT, 39 w/o SCT
- **Expl Non-Cardiac (Control)**: 0 w/ SCT, 6 w/o SCT
- **Cardiac at Rest (Control)**: 0 w/ SCT, 12 w/o SCT

Number of Recruit Deaths
Percent of Exercise Related Recruit Deaths Exposed to Substantial Heat Stress
(Same or Prior Day WBGT ≥ 75°F)

- **SCT** (N = 19): 17
- **EHI** (N = 15): 16
- **ISD** (N = 15): 9
- **SCD** (N = 39): 5
- **Control** (N = 18): 1

Odds Ratio

% Recruit Deaths
Cases of Sudden Cardiac Death with Features of EHI

- Review of 120 recruit cases & 50 additional cases of fatal EHI with SCT
- Eight patients had hyperthermia or typical chemical changes of rhabdomyolysis and a substantial preexisting cardiac lesion.
- Cardiac stress from EHI can provoke fatal complications due to preexisting heart disease.
- Such deaths might be preventable.
HYPOTHESIS

Effective intervention to prevent EHI will reduce exercise-related deaths, especially in recruits w/ SCT

• **POPULATION:** All military recruits entering in 1977-81 before (2.1 million ) and in 1982-1991 during intervention (1.8 million participants and 1.1 million non-participants).

• **DATA:** Information on all exercise-related deaths during training and determination of cause of death.

• **COMPARE:** Exercise-related death rates and estimates of lives saved in the intervention and non-intervention recruit populations.
Intervention for Prevention of EHI During Armed Forces Basic Training

• In the Hot Season, Drill instructors would:
  – record WBGT at least hourly at the exercise site
  – decrease exercise intensity and increase rest cycles as WBGT rises, to minimal effort at 90°F
  – order increased water intake & observe water consumption
  – exercise using light track clothing in hot weather
  – immediate rectal temp, cooling and rehydration with early symptoms “falling out”

• Participating Centers
  – Army, Air Force, Parris Island Marine Corps

• Non-Participating Centers
  – Gt Lakes, San Diego Marine Corps
Data Collection for Military Recruit Deaths

• Talk to each PM officer each season
• Visit each training center periodically
• Obtain list of all deaths
• Full autopsy protocol & toxicology reviewed
• Review of clinical & eyewitness accounts, lab data
• Pathology subspecialty review at AFIP
• WBGT from hourly local airstrip records
• Hb AS cases completed, 80% of others

[Number of deaths predicted from 1977-81 rates]

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Observed</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx &amp; Hb AS: 37,000</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Rx &amp; Hb AA: 1.8 Million</td>
<td>19</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Participating, All</td>
<td>32</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Non-Rx &amp; Hb AS: 12,700</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Non-Rx &amp; Hb AA: 1 Million</td>
<td>10</td>
<td>11</td>
<td>-1</td>
</tr>
<tr>
<td>Non-participating, All</td>
<td>14</td>
<td>15</td>
<td>-1</td>
</tr>
</tbody>
</table>
Non-Participant Exercise-Related Deaths
with Hb AS

• Three/four cases occurred during the hot season.
• WBGT was not measured regularly.
• Opportunity for water drinking was given
• The DI’s did not order or witness the victims drinking.
• They did not follow the major features of our intervention
1. Intervention to prevent EHI eliminated the excess risk of death for 37,000 recruits with sickle cell trait.
2. This included prevention of idiopathic sudden death, implying that EHI was an essential part of these deaths.
3. Effective intervention does not require identification of Hb AS since current diagnosis and treatment do not differ by hemoglobin type.
4. The effect of our intervention on recruits w/o Hb S awaits tabulation of pathology review.
5. Unrecognized exertional heat illness is an important preventable factor contributing to idiopathic and cardiac sudden deaths.
CONCLUSIONS-2

1. Hot weather for 24 hrs before collapse is significantly associated with exercise-related sudden death, with or without heart disease.

2. A study of ER visits by recruits demonstrated that EHI was a more common risk factor than silent heart disease for events requiring ACLS.

2. When young adults suffer exercise-related collapse, heat illness is in the differential diagnosis. A rectal temperature should be measured and stat labs obtained from blood and urine samples. If the patient dies before this was done, early post-mortem body temperature and labs (vitreous humor or urine) are useful.

3. Correction of hyper-K, acidosis, other electrolyte imbalance, hyperthermia, hypoglycemia, and volume needs should accompany ACLS.

4. Oxygen use should be the same as for patients without Hb S.
1. Risk of EHI can be reduced during demanding exercise by awareness that risk increases with poor acclimation, poor conditioning for the planned event, heat retaining clothing, hot weather with high humidity, sunlight, low wind, loss of sleep, dehydration, and heroic effort with disregard for symptoms. An additional risk for sickle cell trait is high altitude (8,000 ft+) or any other cause of hypoxemia.

2. Use of the WBGT index and a trainer can help one to follow a sensible exercise plan.

3. Aggressive hydration cannot compensate for maximal sweating (loss up to 3 L/hr with max fluid intake at 1.5 L/hr). Often reduced intensity and increased rest cycles are needed. Sustained consumption of >1-2 qt per hr may cause hypo-Na.

3. Heat illness can occur in cold weather and without thirst.

4. In the military risk falls with time in service.
The Eichner Hypothesis: Initial sickle crisis causes ERD

- Eichner can recognize a syndrome of muscle sickling crisis in SCT athletes which responds to oxygen and fluids over 10 to 20 minutes.
- With response they can return to competition.
- Most ERD with SCT starts with explosive sickling causing sudden death in minutes.
- These personal observations conflict with our planned multiclinician study at Parris Island.
- Sickle cell disease rarely if ever produces a muscle crisis syndrome and rhabdo survivors do not have focal vascular obstruction.
- Inhaling oxygen shouldn’t improve O2 transport in the absence of an increased A-a gradient.
- He concludes we must identify people with SCT and train them to recognize prodomal muscle crisis events, stop, and receive Rx.
- We conclude that we should use preventive measures for everyone and reduce the pool of people with SCT who develop severe levels of EHI. Screening is often not necessary.
1. What is the mechanism by which SCT increases exercise-related mortality?
2. Does hyposthenuria have a significant effect on this risk?
3. Are there other genetic variants that contribute to these unusual events?
4. Would adjustment of exercise for prior day heat exposure improve outcome or would this be corrected simply by good early morning hydration?
5. Can we produce guidelines for application to athletes who utilize ordinary weather reports?
Alpha-Thalassemia Protects Against Exertional Mortality with Sickle Cell Trait

- 30% of African Americans have alpha-thalassemia (2-3 alpha genes instead of 4). In those with sickle cell trait the main effect is to lower the Hb S fraction below 36% of total Hb.
- Globin monomers are enzymatically destroyed in RBCs. Beta_A-globin is negatively charged, an advantage over Beta_S-globin, in competition to form dimers with alpha-globin.
- We collected 50 cases of exercise-related death/near death with sickle cell trait and Hb S%: we expected 15 cases with alpha-thalassemia & <36% S.
- Two cases had Hb S < 36%, implying about a 7.5-fold protection for those with alpha thalassemia and suggesting that deoxy-HbS polymerization might cause this syndrome.
**Alpha-Thalassemia and Exertional Mortality with sickle cell trait**

- Gupta et al., J Clin Invest 88:1963, 1991 established that hyposthenuria with AS is prevented as alpha globin content falls.
- I found that risk of SD unexplained by preexisting disease increased 8-fold with age for recruits with SCT but there was no age trend for recruits w/o SCT.
- Since hyposthenuria also correlates with age actual studies of exercise-risk as a function of hyposthenuria are needed. These studies were planned, but we found no cases hospitalized with EHI who had SCT.
- We can’t determine the effects of either alpha thal or hyposthenuria on risk of unexplained exercise-related death.
# Numbers of Exercise Related Deaths with Sickle Cell Trait (SCT) by Service, U. S. Military Basic Training

<table>
<thead>
<tr>
<th>Year</th>
<th>Army</th>
<th>Air Force</th>
<th>Marine Corps</th>
<th>Navy</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977-81</td>
<td>6*</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>1982-86</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1987-91</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1992-96</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>1997-2001</td>
<td>1*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

*an additional death from SCD occurred in this period*
Does Rectal Temperature $\geq 106^\circ$F Predict Heat Stroke as Defined by PI score $\leq 4$?

<table>
<thead>
<tr>
<th>Rectal Temperature</th>
<th>CNS Level</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 106^\circ$F</td>
<td>35</td>
<td>71</td>
</tr>
<tr>
<td>$&lt; 106^\circ$F</td>
<td>34</td>
<td>397</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>468</td>
</tr>
</tbody>
</table>

Sensitivity = $\frac{35}{69} = 51\%$

Specificity = $\frac{363}{399} = 91\%$

Predictive Value (+) = $\frac{35}{71} = 49\%$
Cases of Sudden Cardiac Death with Features of EHI

- Review of 120 recruit cases & 50 additional cases of fatal EHI w SCT
- More than 15 patients had hyperthermia or typical chemical changes of rhabdomyolysis and a substantial preexisting cardiac lesion.
- Cardiac stress from EHI can provoke fatal complications due to preexisting heart disease.
- Such deaths might be preventable.
Patients with sickle cell trait who have EHI do not differ in clinical presentation from those who do not. The location and clinical course do not differ initially. Even for those with life threatening complications leaving the ER features specific to sickle cell trait are rarely seen. One can rarely observe episodes of splenic infarction or renal papillary necrosis with hematuria provoked by exercise among people with sickle cell trait. This is the only sickling specific syndrome I know of. It is seldom associated with severe EHI, except for people with sickle cell disease, who can have prolonged progressive complications. Even at high altitude these complications are very rarely life threatening for people with sickle cell trait.
Advice to People with SCT

After becoming well conditioned, risk of unexpected exercise-related death is much less, but still significant.

The same precautions should be taken to avoid heroic effort, to remain conditioned for any task, and to follow sensible procedures to minimize risk of EHI at all times.
1982-91 Recruit Heat Illness Rates by Gender and Month

Rate per 1000 person-months

- Male
- Female
Effect of Sickle Cell Trait on Rates of Non-Fatal Exertional Heat Illness

- Collected all cases of EHI at Parris Island among African American recruits for 3 yrs.
- The incidence of EHI was 0.55% of 1,500 recruits with hemoglobin AS.
- The incidence of EHI was 0.54% of 36,325 recruits without hemoglobin S.
- Sickle cell trait did not appear to alter the risk of non-fatal exertional heat illness.
Rates of Exertional Heat Illness
Among Parris Island Recruits 1979-1991
(excluding 20 cases w life-threatening complications)

<table>
<thead>
<tr>
<th>Category</th>
<th>Observed</th>
<th>Population</th>
<th>Rate/1000</th>
</tr>
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<tbody>
<tr>
<td>Mild &amp; Hb AS</td>
<td>32</td>
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<td>6.1</td>
</tr>
<tr>
<td>Hospitalized &amp; Hb AS</td>
<td>&quot;2&quot;</td>
<td>5010</td>
<td>0.40</td>
</tr>
<tr>
<td>Hospitalized &amp; No Hb S</td>
<td>225</td>
<td>262728</td>
<td>0.86</td>
</tr>
</tbody>
</table>
The Utility of Screening for SCT

The diagnosis and management of EHI is identical for those with or without SCT.

While knowledge that one has SCT can motivate a person to better protect themselves from EHI, a beneficial effect on behavior or medical outcome has not been demonstrated. SCT Mortality has varied widely irrespective of screening policy.

In our prospective study 35,000 Army recruits with SCT completed basic training without deaths in the absence of expensive screening for SCT.
The Utility of Screening for SCT

The main advantage of screening for SCT would be the detection of recruits with unrecognized sickle cell disease, because of mild or undisclosed cases.

Since recruits with SCD are at high risk of developing serious or fatal sickle crisis episodes from mild EHI, it would be important to complete screening prior to any PT.

The cost of not screening for SCD involves not only the loss of personnel but the expense of investigations of hospitalizations and training deaths. These may have major legal implications and potential impact upon the military careers of all training personnel.
Screening for Sickle Cell Trait and Sickle Cell Disease

2. CBC - normal for Hb AS, anemia with increased RDW for 97% of sickle cell disease.
3. Quantitative Hemoglobin electrophoresis in alkali.
4. Reticulocyte count elevated in 97%+ of SCD but normal in uncomplicated Hb AS.
Exertional Heat Illness as a Risk Factor for Threatened or Actual Sudden Death

<table>
<thead>
<tr>
<th></th>
<th>Exertional Heat Stroke</th>
<th>Without Heat Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td>7 (2d)</td>
<td>4 (4d)</td>
</tr>
<tr>
<td>Population at risk</td>
<td>137</td>
<td>267,000</td>
</tr>
<tr>
<td>Case Rate</td>
<td>5.1%</td>
<td>0.0015%</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>3,400</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>
# Etiology of Exercise-Related Deaths

Kark JA & Ward F Semin Hematol 1994; 31:181-225  

<table>
<thead>
<tr>
<th>Condition</th>
<th>Military</th>
<th>Athletes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explained Cardiac Death</td>
<td>44%</td>
<td>75% (73)</td>
</tr>
<tr>
<td>Explained non-Cardiac Death</td>
<td>6%</td>
<td>3% (5)</td>
</tr>
<tr>
<td>Exertional Heat Illness</td>
<td>27%</td>
<td>1% (15)</td>
</tr>
<tr>
<td>Idiopathic Sudden Death</td>
<td>23%</td>
<td>12% (5)</td>
</tr>
<tr>
<td>Sickle Cell Trait</td>
<td>20%</td>
<td>0.2% (5)</td>
</tr>
</tbody>
</table>
Percent of Exercise Related Recruit Deaths Exposed to Substantial Heat Stress
(Same or Prior Day WBGT $\geq 75^\circ$F)

<table>
<thead>
<tr>
<th>Group</th>
<th>% Recruit Deaths (N)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCT</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>EHI</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>ISD</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>SCD</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Control</td>
<td>18</td>
<td>1</td>
</tr>
</tbody>
</table>
Cases of Sudden Cardiac Death with Features of EHI

- Review of 120 recruit cases & 50 additional cases of fatal EHI w SCT
- More than 15 patients had hyperthermia or typical chemical changes of rhabdomyolysis and a substantial preexisting cardiac lesion.
- Cardiac stress from EHI can provoke fatal complications due to preexisting heart disease.
- Such deaths might be preventable.
Objectives

1. Analyze autopsy-determined specific mortality rates of a defined recruit population to determine whether sickle cell trait (Hb AS) is a risk factor for death from exertional heat illness (EHI).

2. Describe major risk factors for non-fatal EHI among a defined recruit population.

3. Determine the contribution of EHI to life-threatening cardiovascular complications of exercise among the same recruit population for non-Hb S and Hb AS recruits.

4. Interpret results of a controlled prospective intervention to prevent EHI on exercise-related mortality of recruits with or without Hb AS.

5. Provide practical recommendations for the safer management of exercise by young adults with or without HbAS.
Implications from Sickle Cell Trait for Exercise-Induced Heat Illness: Policies to Prevent Exercise-Related Death

John A. Kark, MD
from studies with
John W. Gardner, MD, DrPH
Frank T. Ward, MD
Renu Virmani, MD

Howard University Center for Sickle Cell Disease
Uniformed Services University of the Health Sciences
Walter Reed Army Medical Center
Armed Forces Institute of Pathology
Screening for Sickle Cell Trait and Sickle Cell Disease


2. CBC - normal for Hb AS, anemia with increased RDW for 97% of sickle cell disease.

3. Quantitative Hemoglobin electrophoresis in alkali.

4. Reticulocyte count elevated in 97%+ of SCD but normal in uncomplicated Hb AS.
Key Points

• Severe exertional heat illness:
  – can occur in cool weather
  – can occur without high body temperature
• Mental status change
  – may reflect severe illness
• Vital signs & Laboratory values
  – must be closely monitored
  – early rapid cooling essential
• Dehydration & Acidosis
  – early & aggressive IV therapy
• Sickle Cell Trait Patients
  – have higher risk of death
Clinical Features of Sickle Cell Disease

Hemolytic anemia & other types of anemia
• Median Hb about 8 g/dL w intra-vascular component, Acute anemia: folate depletion, Parvovirus B19 & other infection, splenic sequestration, high rate of delayedtxn rxns, G6PD deficiency, chronic: low EPO, iron deficiency

Infectious complications
• Bacteremia/meningitis w encap’d organisms (esp <5 yrs), pneumonia, Osteomyelitis (Salmonella, Staph aureus), Urinary tract infections, port infections

Vaso-occlusive pain episodes

Cholelithiasis: salmonella carriage, stones
Vasoconstriction from low NO: Pulm HTN, skin ulcers
Thrombotic and hemorrhagic strokes
Chronic organ damage
Increased mortality
Screening for Sickle Cell Trait and Sickle Cell Disease

- Sickle cell screen: Place blood drop in phosphate buffer: Hb S precipitation: high specificity and sensitivity.
- CBC - normal for Hb AS, anemia with increased RDW for 97% of sickle cell disease.
- Quantitative Hemoglobin electrophoresis in alkali.
- Reticulocyte count is elevated in 99%+ of SCD but normal in uncomplicated Hb AS.
- Rarely right to left cardiac shunts or increased BPG confer a disease phenotype with Hb AS.
How do we prove that a medical complication was caused by “sickling” from Hb AS?

- At biopsy or autopsy agonal hypoxia may cause extensive sickling despite no causal role.
- We must show a significant relative risk for people with Hb AS versus those w/o Hb S from the same population.
- *Since alpha-thalassemia reduces Hb S, a decrease in rate or severity of a complication as the number of alpha genes decrease implies quantitative dependence of a complication upon the amount of deoxy Hb S.*
- Proof applies to populations not to individuals.
## Odds Ratios Combining PFT1 Run Time and BMI Category for Exertional Heat Illness, Male Marine Recruits, MCRD-PI, 1988-1992

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>1.5 Mile PFT1 Run Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10 minutes</td>
</tr>
<tr>
<td>&lt;22 kg/m²</td>
<td>1.0</td>
</tr>
<tr>
<td>22-&lt;26 kg/m²</td>
<td>1.6</td>
</tr>
<tr>
<td>26+ kg/m²</td>
<td>3.7</td>
</tr>
</tbody>
</table>