Anemia to Blood Doping: Hematologic Issues in Athletes

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Objectives

- Identify iron deficiency without anemia in athletes
- Recognize the risk of sickle cell trait in the athletic population
- Review the techniques used in blood doping
Iron Deficiency
Iron deficiency

• Anemia: for women, <12.0; for men <14.0

• Latent anemia:
  – Serum Fe: 60-170 mcg/dl
  – TIBC: 240-450 mcg/dl

• Pre-latent anemia:
  – Ferritin: Women < 10; men < 20
  – Ferritin in athletes: < 20(?); < 30(?)
How common is the problem?

• Prevalence of inadequate iron balance:
  – Male athletes: up to 10%
  – Female athletes: up to 20%
Why?

- Menstrual losses
- Diet
  - CHO diet
  - Increased transit time through gut
- NSAIDs
- Sweat losses
- Foot strike hemolysis
- G-I losses

Role of Fe

DNA synthesis

Electron transport

Component of hemoglobin (O₂ transport), myoglobin
The Hemoglobin Molecule

Hemoglobin Molecule

- red blood cell
- α chain
- β chain
- helical shape of the polypeptide molecule
- iron
- heme group

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Electron transport

Key role in anaerobic metabolism.
Measuring storage iron

• Ferritin
  However, ferritin is an acute phase reactant and may be affected by acute illness and recent, intense workouts.

Soluble transferrin receptor (sTfr)
  Levels > 2.8 mg/L more sensitive and specific for iron deficiency than low serum ferritin. Not an acute phase reactant.
Ferritin vs soluble Transferrin receptor?

Cost differential??
Treatment

- If asymptomatic and ferritin < 20, consider therapeutic iron replacement.
- If symptomatic and ferritin < 30, consider iron replacement.
- Monitor hgb. If hgb increases by about 1 gram over the course of 4-6 weeks of therapy, iron Rx was appropriate.
- If no increase in hgb, consider ferritin and hgb levels as physiologic adaptations.
Sickle Cell Trait
SCT Facts

• Approximately 3 million people in the US and 300 million around the world have SCT.
• The presence of SCT appears to be protective against severe falciparum malaria.
• Prevalence in the US:
  African Americans: 1/14 (7%)
  Hispanic/Latino: 1/183 (0.04%)
  Caucasians: 1/625 (0.0016%)
• 4/10 West Africans have SCT!
• Newborns are already screened for SCT
A little about Sickle Cell Trait

Hb AA
Hb AS

Normal Red Blood Cells
Sickled Red Blood Cells

Normal red blood cells are compact and flexible, enabling them to squeeze through small capillaries.

Sickled red blood cells are stiff and angular, causing them to become stuck in small capillaries.

Normal hemoglobin
Sickle Cell hemoglobin forms long, inflexible chains

A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel

B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow

Sticky sickle cells

Cross-section of RBC
Normal hemoglobin

Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape
SCT is associated with sudden death!

• Exertional sickling can be fatal
• 2000-2010, 16 deaths occurred in NCAA sports, 10 were related to SCT

During conditioning!

• From a different perspective: 16 deaths occurred (4 cardiac, 1 asthma, 1 EHS). SCT, which affects only about 3% to 4% of all NCAA Division 1 football players, accounts for 63% of the deaths.

The Circumstances

- Sickling collapse is an *intensity* syndrome

- The “perfect storm” for sickling collapse
  - SCT (+)
  - Brief, but intense exertion (most 2-30 minutes)
  - Effort beyond current fitness capability

- It seems the harder and faster athletes with SCT go, the earlier and greater the sickling
- Dehydration increases exertional sickling
- Altitude is a risk factor for exertional sickling.
The Clinical Picture

- **SCT Collapse**
  - Weakness > pain
  - Slumps to ground
  - Can talk at first
  - Muscles “normal”
  - Temp < 103° F
  - Early in exercise

- **Cardiac Collapse**
  - No cramping
  - Falls suddenly
  - Unconscious
  - Limp or seizing
  - Temp irrelevant
  - No warning
The Clinical Picture, Part II

- **SCT Collapse**
  - Weakness > pain
  - Slumps to ground
  - Can talk at first
  - Muscles “normal”
  - Temp < 103° F
  - Early in exercise

- **Heat Stroke**
  - Fuzzy thinking
  - Bizarre behavior
  - Incoherent
  - Can be in coma
  - Temp often > 106°F
  - Usually occurs late
The Clinical Picture, Part III

- **SCT Collapse**
  - Weakness > pain
  - Slumps to ground
  - Can talk at first
  - Muscles “normal”
  - Temp < 103° F
  - Early in exercise

- **Asthma**
  - Usually known asthma
  - Prior episodes, poor control
  - Breathless, may wheeze or not
  - Gasping, panicky, on hands/knees
  - Auscultate: moving little air
  - Usually occurs after sprinting
NCAA - The Background

- 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 in part a result of legal settlement with Dale Lloyd II case.
Testing Implications

Assuming a 100 percent effective intervention, this screening program requires that 144,181 student-athletes be screened to prevent one death.

Cost of testing: range from $1,441,810 to $2,883,620 for sickle cell solubility testing and about $106,150 for hemoglobin electrophoresis.

There may be as many as 22 false negative tests, carriers misidentified as negative.

Sport-Specific Training

• Consider the usual football game...
In a typical National Football League game, the ball is in play for only 11 minutes
Average play lasts 4 seconds, and 40 seconds are then allowed to snap the ball again
Work:rest ratio for players is 1:10
Football comprises brief bursts of all-out action with long interim rests
• Does this reflect the type of conditioning for football?
Other SCT consequences

In football, for every fatal sickling collapse, 3-5 nonfatal collapses occur, involving lumbar paraspinal myonecrosis, splenic infarction at altitude, or leg compartment syndrome as reported also in military with SCT, and some involving rhabdomyolysis, acute renal failure, renal dialysis, and up to 2 months in the hospital for rehabilitation.
Treatment

- Check VS
- Supplemental oxygen
- Cool, if indicated
- Call 911
- Attach AED
- IV fluids
- Transport to ED
- Alert ED possibility of rhabdomyolysis
Prevention

- Athletes with SCT should set their own pace.
- Athletes with SCT should build up slowly in training, with paced progressions and longer breathers (rest spell).
- Extreme performance tests should be avoided.
- Athletes with SCT should stop immediately upon struggling, or upon any unusual muscle pain or weakness, "cramping," breathlessness, discomfort, or undue fatigue.
- Predisposing factors include heat, altitude, dehydration, asthma, and other illness, because they make any workout harder.
Athletes with SCT can excel

- SCT carriers of the Ivory Coast of Africa established 32/33 records at distances up to 400 meters

- Suggests success in high intensity, short distance events

- Athletes with SCT successfully competed in the 1988 Olympics in Mexico City at an elevation of 5000 feet.
Blood Doping (Building)

“Hey, I’m not accusing anyone of anything. I’m just saying he never even slows down on hills, and it raises red flags.”
Benefits

• Increased RBC mass


• 9% Increase in VO$_2$ max

• Increased running time to exhaustion by 23%
Homologous, Autologous, EPO

- 1984 US cycling team
- Cycling, in general
- Olympics
  - Lasse Viren

- Blood doping is defined by the World Anti-Doping Agency (WADA) as the use of products that enhance the uptake, transport, or delivery of oxygen to the blood
- Banned in 1986
Transfusion

- 6-12 weeks prior to a “competition”, 500-1800 mL of blood removed.
- Blood is centrifuged. Packed RBC’s stored. Plasma re-infused.
- Packed RBC’s re-infused 6-7 days prior to the event.

Risks
- Reduced, training capability
- Blood-borne infections
- Polycythemia (erythrocythemia) and potential complications of increased viscosity
EPO

• Procedure
  – Inject recombinant EPO

• Risks
  – Unpredictable response
  – Complications of increased viscosity
  – Between 1987-1990, 19 Dutch and Belgian cyclists died of unexplained causes
Biological Passport

• Use of biomarkers that infer use of prohibited substances, especially EPO
• Adopted by WADA 2009

  – Purpose
    • Identify and target athletes for specific analytical testing (examples – EPO urine test, homologous blood transfusion test)
    • Pursue antidoping rule violations
Summary
Bibliography