Similarities of Exertional Heat Stroke, Malignant Hyperthermia and Rhabdomyolysis – How might EAH Play a Role?

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The Paradox: Exertional Heat Stroke

- In hazardous environmental conditions not all athletes are at the same risk of developing EHS
- Why will one athlete an any given day succumb to EHS when others at the same site are unaffected?
- Why will one athlete develop EHS in environmental conditions that should be ideal for exercise?
- Answers to these questions are still unknown as we do not understand the exact causes for EHS
- But we do know there are links to Malignant Hyperthermia and Rhabdomyolysis – and now EAH

Topics for this Talk

- Common Factors associated with EHS
- Pathophysiology of EHS
- Predisposing Factors not often discussed related to EHS
  - The link between MH, EK, EHS and EAH
- Athletes at most risk for EHS
- Reasons leading to a fatal outcome from EHS
- Proper treatment to avoid a fatal outcome

Predisposing Factors to EHS

- Environmental
- Organizational
- Individual Physiologic Limitations
  - Raw-Adas Am J Med 2004

Environmental Factors

- Heat Load corresponding to WBGT ≥ 27 °C (81°F)
- High Solar Radiation
### Organizational Factors
- Physical effort unmatched to physical fitness
- Improper work/rest cycles
- Minimal access to fluids
- Absence of proper triage
- Training at the hottest hours disregarding regulations

### Individual Physiologic Limitations
- Underlying Illness
- Low Physical Fitness
- Dehydration
- Sleep deprivation
- Overweight
- Improper Acclimatization

### Prevalence of Factors in Fatal versus Nonfatal Cases of EHS

<table>
<thead>
<tr>
<th>Predisposing Factor</th>
<th>% of Fatal Cases (n=60)</th>
<th>% of Non Fatal Cases (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat Load (WGST) &gt; 27°C</td>
<td>83%</td>
<td>16.5%</td>
</tr>
<tr>
<td>High Solar Radiation</td>
<td>83%</td>
<td>35%</td>
</tr>
<tr>
<td>Physical effort unmatched to Fitness</td>
<td>100%</td>
<td>21.6%</td>
</tr>
<tr>
<td>Improper Work/Rest Intervals</td>
<td>67%</td>
<td>24%</td>
</tr>
<tr>
<td>Improper Hydration Regimen</td>
<td>50%</td>
<td>16%</td>
</tr>
<tr>
<td>Absence of Medical Triage</td>
<td>100%</td>
<td>15%</td>
</tr>
<tr>
<td>Training in Hottest Hours</td>
<td>67%</td>
<td>35%</td>
</tr>
</tbody>
</table>


### Additional Risk Factors
- Equipment/barriers to evaporation
- History of heat intolerance
- Drugs/Medications/supplements
  - Stimulants, ephedra, ADHD meds, Caffeine?
- Anhidrosis

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Additional Risk Factors

- Male Gender
  - In 2069 Marine Corp Recruits suffering from EHI, 11% were female
  - In 650 hospital visits for EHI in Marine Corp recruits, 85% were female but none severe enough to require hospitalization
  - 5.0% of all nontraumatic exercise related deaths in U.S military from 1996-1999 were EHS, none female
  - In all of the human case studies of EHS, MH or ER reviewed for this presentation, none were female

Are all Athletes at risk for EHS?

- There has been only a few documented cases of a female dying of Exertional Heat Stroke
  - Hormonal??
  - Females listen to their Brains!!
  - Genetics

Are all Athletes at Risk for EHS?

- Exertional Heat Stroke is largely a post-pubescent male issue
- Strong evidence to support a genetic link
- All familial ties in the malignant hyperthermia case studies with RyR1 mutations were male

Little Known Factors not Often Discussed

- The link between:
  - Malignant Hyperthermia
  - Exertional Rhabdomyolysis
  - Exertional Heat Stroke
- Other Internal Factors
  - Underlying Illness
  - How can exercise associated hypotension play a role?

Ryanodine Receptor 1 (RYR1) is the skeletal muscle calcium release channel. In humans, it is encoded by the RYR1 gene.

What is the role(s) of ATP??

Ca** released from SR

Ca** released from SR
Pathophysiology of EHS

- EHS differs from Classical Heat Stroke
- EHS is a life-threatening syndrome of:
  - Rapid Hyperpyrexia (Te > 104°F)
  - Rhabdomyolysis
  - Hyperkalemia
  - Metabolic acidosis
- The cause(s) are multifaceted and complicated

Pathophysiology of EHS

- Musculoskeletal Injury – muscle tissue necrosis and rhabdomyolysis** leading to renal failure
- Blood – decreased blood coagulation with potential hemorrhage following disseminated intravascular coagulation
- Decreased exercise heat tolerance – ranges from short-term disturbances to lasting inability to acclimatize and tolerate exercise in the heat

Pathophysiology of EHS

- CNS Involvement – always present initially and temporary with rapid cooling
- Liver Injury – ranges from slight anoxic injury to total hepatic failure
- Renal Injury – ranges from temporary oliguria to acute renal failure. Temporary renal dysfunction is common and reversible
- Cardiac Injury – cardiomyopathy ranges from temporary electrical disturbances to MI
Acute Phase – the Golden (1/2) Hour
- EHS always results in CNS dysfunction
  - Altered consciousness
  - Irritability/agitation
  - Mental confusion
  - Stupor
  - Feelings of hyperthermia

Blood and Enzyme Phase
- Hours 2 through 48
- Characterized by blood and enzyme changes
- Blood disorders include:
  - Leukocytosis
  - Endotoxemia – gram negative bacteria
  - Elevated WBC count
  - Hyperkalaemia
  - Hypercalcemia
  - Disseminated intravascular coagulation

Blood and Enzyme Phase
- Enzyme elevation due to organ damage:
  - Alanine aminotransferase
  - Aspartate aminotransferase
  - CPK
  - Lactate dehydrogenase

Late Phase
- Hours 12 through 72
- Characterized by liver and kidney dysfunction due to rhabdomyolysis
- Myoglobin released into bloodstream degrades to chemical substances that are toxic to renal cells
- Elevated enzymes (transferases) indicates liver failure
- Cardiac function can also be impaired

Animal Models for researching MH
- Research in Malignant hyperthermia was limited until the discovery of porcine stress syndrome
- A genetic syndrome in certain pig breeds known for poor quality of meat
- These pigs have a (single) RyR1 gene mutation and will have MH triggered by halothane
- Horses can also have MH, EHS and ER
Malignant Hyperthermia

- MH is an uncommon, dominantly inherited disorder of Ca^{++} handling in skeletal muscle.
- It is mainly caused by mutations in the gene coding for the type one Ryanodine receptor (RyR1).
- MH is a potentially fatal, pharmacogenetic disorder induced or triggered by inhaled volatile anesthetics (halothane or isoflurane).

Malignant Hyperthermia

- A fulminant MH episode or crisis results from rapid and sustained rise in myoplasmic Ca^{++}.
- This rapid and uncontrolled rise in muscle cell Ca^{++} constitutes a hypermetabolic state which leads to:
  - Hypercapnia, tachycardia and metabolic acidosis
  - Muscle rigidity—leads to structural membrane damage and the release of intracellular substances
    - CK, lactate dehydrogenase, myoglobin and potassium

Malignant Hyperthermia

- Extreme hyperthermia is a late sign and the consequence of the hypermetabolic state.
- Dantrolene, a compound that blocks release of calcium from the SR via the RyR1, can provide effective treatment.
- Without Dantrolene and rapid cooling, mortality from "fulminant" episodes exceeds 70%.

Malignant Hyperthermia

- MH is characterized by its variability.
- MH susceptible individuals do not develop episodes with every exposure to anesthetic drugs.
- Some individuals need more than one exposure before an acute MH event occurs.
- Some individuals have reported spontaneous episodes without any exposure to anesthetic drugs.

MH Diagnosis

- The diagnosis of MH is typically based on a personal or family history of a clinical MH episode during anesthesia, or
- A positive response to a muscle biopsy test.
- Muscle fibers from MHS individuals are markedly more sensitive to RyR1 agonists.
Muscle Contracture Tests for MH

- In N. America, a positive response to the caffeine halothane contracture test (CHCT) is done with muscle biopsy
- This test is used to diagnose patients as MH susceptible (MHS) or MH-normal (MHN)

Malignant Hyperthermia

- Males are more frequently affected than females
- A muscular build appears to be a predictor risk factor for MHS
- Family history most often involves father or brother

MH and EHS

- Malignant hyperthermia is a human stress syndrome of which many researchers now believe Exertional Heat Stroke is one manifestation
- Equine case studies support the same link between MH and EHS and a mutation of the RyR1 receptor

Exertional Rhabdomyolysis

- ER is a syndrome characterized by destruction of the skeletal muscle cell membrane resulting in massive release of intracellular CK, K⁺, myoglobin, and other intracellular constituents.
- ER can occur from strenuous physical activity, particularly eccentric exercise when mechanical or metabolic stress damages muscle fibers.

Exertional Rhabdomyolysis

- ER can occur in the absence of high environmental temperatures
- It is also seen as a consequence of exertional heat stroke, coexisting with sickle cell trait or use of dietary supplements
- Those at risk for exertional rhabdomyolysis
  - Military recruits, long distance runners, weight lifters and football players
  - This also plagues the equine world

ER Diagnosis

- A serum CK level ≥ 5 times normal
- Urine analysis positive for myoglobinuria
- CK levels may peak between 12 and 96 hr after exercise and then decline progressively.
- Musculoskeletal pain typically occurs 24 - 48 hr after extreme or non-familiar exercise
- Mahogany colored urine is a primary sign
Human Case Studies of EHI and MHS

<table>
<thead>
<tr>
<th>Author</th>
<th>Reason for Workup</th>
<th>Total Patients</th>
<th># MHS</th>
<th># MH1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackie et al. 1991</td>
<td>EHI</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hopkins et al. 1991</td>
<td>EHI</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Ogilvie et al. 1995</td>
<td>EHI</td>
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<td>1</td>
<td>0</td>
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<tr>
<td>Fignaud-Braugere et al. 1993</td>
<td>EHI</td>
<td>45</td>
<td>13</td>
<td>26</td>
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<tr>
<td>Hunter et al. 1987</td>
<td>EHI</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Kochling et al. 1998</td>
<td>EHI</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Bencze et al. 2007</td>
<td>EHI</td>
<td>20</td>
<td>26</td>
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<tr>
<td>Fink et al. 2006</td>
<td>EHI</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>82</td>
<td>53 (65%)</td>
<td>29 (35%)</td>
</tr>
</tbody>
</table>

Human Case Studies of ER and MHS

<table>
<thead>
<tr>
<th>Author</th>
<th>Reason for Workup</th>
<th>Total # patients</th>
<th># MHS</th>
<th># MH1</th>
<th>Patients With RyR1 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegler et al. 2001</td>
<td>Rhombo</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td><strong>3</strong></td>
</tr>
<tr>
<td>Davis et al. 2002</td>
<td>Rhombo</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Leis et al. 2006</td>
<td>Rhombo</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rosenblatt et al. 2002</td>
<td>EHS</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>17</td>
<td>15</td>
<td>2</td>
<td><strong>8 (47%)</strong></td>
</tr>
</tbody>
</table>

**Note:** A negative RyR1 genotypic screen with a positive clinical history does not necessarily mean that the patient does not have a mutation that is yet unidentified.

Case Study: 12 Year Old Boy

- Had MH episode triggered by anesthesia during surgery to reduce a humeral fracture
- Had maximal CK level of 9,000 U.L⁻¹
- 8 months later while participating in a football game in ambient temp = 108°F
- Had fatal EHS (Tc = 108°F, serum K⁺ = 8.8mEq.L⁻¹)
- Both he and his father had RyR1 gene mutation

RyR1 Variants in African American Men with ER and MHS

- 6 unrelated healthy men of African descent
- All experienced a single or recurrent episodes of exertional rhabdomyolysis
- All were positive for MHS by CHCT
- All had RyR1 sequence variants but 3 of the 6 had novel variants not previously known
- Additionally, 3 of the 6 had multiple RyR1 variants

Equine Case Studies

Malignant Hyperthermia Associated with RyR1 Mutation in Quarter Horses

- 11 horses, 10 with markedly prominent muscle mass
- All 11 had an RyR1 mutation
- 5 horses died during inhalation of anesthesia (halothane or isoflurane)
- 4 horses died as a result of exertional rhabdomyolysis
- 2 horses survived rhabdomyolysis
MH, EHS and ER

- What are the exact similarities?
- Do they share common or parallel pathways to a systemic inflammatory response?
- How does exertional rhabdomyolysis fit into the picture?
- How can exercise associated hyponatremia be linked to rhabdomyolysis?

Case studies on EAH and Rhabdo

What about Underlying Illness

- 21% of the non-fatal cases but 50% of the fatal EHS cases involved underlying illness as reported by Rav-Acha
- A case study of Marine Corp recruits, all 4 subjects with EHS had prodromal symptoms (3 with URI 2-4 days prior to the event and 1 with a fever 2 days prior to the EHS episode)
Factors Contributing to Fatal Outcome
- Improper recognition and or diagnosis
- Delayed or improper treatment

EHS and EAH can Occur Together
- Why do some people over-drink before, during and/or after exercise?
- It does not prevent EHS -- the link to Rhabdo might actually contribute to it in some cases!
- Soldier who had a fatal outcome from BOTH EHS and EAH.

Recognition & Treatment of EHS
- Recognition and prompt treatment are the key!!
- We probably can't prevent all EHS BUT
- We can prevent A Fatal outcome

Recognition of EHS
- Rule out precipitating factors such as illness, fever, vomiting or diarrhea
- Are they large in size
- Are they taking a lot of reps during practice
- Did they go through the proper period for heat acclimatization

Signs and Symptom of EHS
- They feel hot to the touch
- They tell you that they are burning up
- Irritability
- Agitation
- Confusion
- Conscious but lacks responsiveness"Out on their feet"
Recognition of EHS

- Rule out other causes of CNS impairment
  - MTBI
  - Exercise Associated Hyponatremia
  - Hypoglycemia
- Did they sustain a head injury?
- Did they Drink Too Much!!
- Are they diabetic?

Treatment

- It's not how HOT - it's how long Tc is above a critical temperature
- Cold water immersion (CWI) is recommended by NATA and ACSM for EHS
- Case studies have reported a 0% fatality rate with 276 EHS patients in the military

Individual Data - Change in Tc over time using CWI (10°C)

- Time to reach 37.5
  - FB group = 11.2 ± 3.9 min
  - DC group = 7.7 ± 1.8 min (p = 0.047)

Practical Applications

- Data from this study recommends:
  - A smaller, lean individual should be aggressively cooled for approx. 7 min in 10°C
  - A larger individual (128 kg, 28% body fat) should be aggressively cooled for approx. 11 min in 10°C water
- Different water temperatures have been shown to elicit different cooling times Prouds et al.

Summary

- Recent data from case studies and case series reports indicates a strong link between exertional heat stroke, malignant hyperthermia and exertional rhabdomyolysis
- A mutation of the RyR1 receptor is a common finding of all three syndromes
- Porcine and equine studies support the RyR1 link reported in humans

Summary

- Abnormal IVCT or CHCT are found in patients with EHS
- For some subjects, but not all, family members also had abnormal contracture tests
- A family member with abnormal CHCT are most often male (father or brother)
- Other factors such as physical stress or heat have been recognized to induce MH
**In HEAT**

Heat Illness Evaluation, Assistance, and Treatment

**Summary**

- In a large (n=250) non-invasive study using magnetic resonance spectroscopy to investigate muscle energetics results support similarities between EHS and MH.
- 73% of EHS patients had an average of 6 metabolic abnormalities indicating susceptibility to MH.

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**Summary**

- EHS subjects may have an underlying skeletal muscle abnormality that is probably distinct from MH but involves similar Ca^{++} disregulation.
- Altered Ca^{++} regulation explains both in vitro abnormal contracture tests and in vivo heat stroke with strenuous exercise.
- "MH is a more general stress-induced syndrome of which heat stroke could be one manifestation."

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**Summary**

- What should we do with this information?
- CHCT is intrusive (muscle biopsy).
- Genetic testing is extremely expensive.
- Magnetic resonance spectroscopy for detection of early acidosis and abnormal muscle energetics may be promising.

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**Summary**

- Clinical importance
- You may want to add questions on your medical history forms:
  - Have you or any of your family members had exertional rhabdomyolysis?
  - Have you or any of your family members had an adverse reaction (MH) to inhaled anesthetics?