Objectives

At the end of this presentation, participants should understand
1) How to recognize exertional rhabdomyolysis as well as contributing factors
2) How to evaluate, manage & make return to play decisions after exertional rhabdomyolysis
3) What can be done to prevent exertional rhabdomyolysis

Introduction

- Incidence of exertional rhabdomyolysis is increasing (MSMR 2012)
- Links to Sickle Cell Trait, Supplement use, Heat Stress, as well as complications of renal injury & death make this an important injury/illness for Team Physicians to understand
- Controversy re: when to hospitalize and when to consider return to play (RTP)

Take Home: Exertional Rhabdomyolysis is the breakdown of muscle related to either mechanical or metabolic insult; "Novel overexertion; doing too much, too fast of an exercise too new" (Eichner '08)

Definition

- Exertional Rhabdomyolysis is the result of acute muscle fiber necrosis leading to cell lysis and the build-up and release of myoglobin as well as electrolytes and intracellular proteins into the circulatory system.
- Rhabdomyolysis can be caused by diseases, injuries (trauma), medications (statins, ecstasy, cocaine) and toxins (alcohol, snake/spider bites), but ER by definition, is related to exertion.
- The most common complications include hyperkalemia, hypernatremia, lactic acidosis, myoglobinemia & myoglobinuria, and hyperphosphatemia. Less commonly Disseminated Intravascular Coagulation (DIC), renal failure (4-33%), and compartmental syndrome can occur. Metabolic abnormalities & acute renal failure are primary determinants of morbidity and mortality
- Myoglobin is filtered by the kidney and therefore in excess accumulation in the kidney is the most significant complication. Renal failure is not common, but can account for 8-10% of all renal failure and thus is an important consideration.

Mechanisms; Mechanical & Metabolic (from O’Conner Sutton Lecture, May ’12)

<table>
<thead>
<tr>
<th>Mechanical Injury</th>
<th>Metabolic injury</th>
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<tbody>
<tr>
<td>Compression</td>
<td>Metabolic myopathies</td>
</tr>
<tr>
<td>Ischemia</td>
<td>Drugs/toxins</td>
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<tr>
<td>Excessive contraction</td>
<td>Infections</td>
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<tr>
<td>Electrical injury</td>
<td>Electrolytes</td>
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<tr>
<td>Hyperthermia</td>
<td>Endocrine Disorders</td>
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</table>

Mechanisms: Mechanical & Metabolic

Or

↑↓ intra-cellular ATP

↑↓ Sarcoplasmic Ca" influx

↑↑ Phospholipase A2
↑↑ Ca++ dependent phosphorylases
↑↑ Nucleases, proteases
↑↑ Free radicals
↑↑ Local PMN cells

RHABDOMYOLYSIS
**Pathophysiology:** impairment of either ATP production or utilization. Muscle injury results in release of K⁺, uric acid, calcium phosphate, **myoglobin** and muscle enzymes (**CK**, LDH, AST, ALT) into plasma


<table>
<thead>
<tr>
<th>Exercise Factors</th>
<th>Non-Exercise Factors</th>
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<tbody>
<tr>
<td>Experience / fitness level</td>
<td>Illness</td>
</tr>
<tr>
<td>Intensity of exercise</td>
<td>Sickle Cell Trait</td>
</tr>
<tr>
<td>Duration</td>
<td>High Ambient Temperature</td>
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<tr>
<td>Type of exercise</td>
<td>Dehydration</td>
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<tr>
<td></td>
<td>Fasting</td>
</tr>
<tr>
<td></td>
<td>Drugs (eg cocaine, ecstasy, statins, alcohol)</td>
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<tr>
<td></td>
<td>Nutraceuticals (eg dimethylamylamine DMAA)</td>
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<tr>
<td></td>
<td>Myopathies</td>
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</table>

Some inherited metabolic disorders can increase risk for ER including:

- Carnitine palmitoyl transferase (CPT2) deficiency
- Myophosphorylase deficiency (McArdles disease)
- Malignant hyperthermia (ryanodine receptor type I/RYR1 gene)
- Sickle Cell Trait

**Level of creatine kinase (CK)** used to define ER remains unclear. **Not always symptomatic with elevated CK levels and vice versa.** Varying levels of CK used to make diagnosis.

- Likely spectrum of ER from asymptomatic physiologic response to clinically relevant and symptomatic disease with complications or underlying pathology. Variability of presentation most likely due to individual factors, volume of muscle involved, individual and external factors
- Must consider what is “normal” level of CK in athletes (Mougios ’07), considering **gender and ethnicity** (O’Connor). Males higher than females, Af Americans higher than other ethnicities.
- Can see elevated CK levels in marathon runners without any symptoms/renal failure, and can also see renal failure in setting of CK < 5000 (Clarkson ’07).
- Broad range of CK levels in response to same level of exertion (Clarkson ’05, Hubal ‘10) with genetic polymorphisms as partial explanation (Landau ’12)

**Table 2.** modified from Mougios BJSM, 2007

<table>
<thead>
<tr>
<th>Reference limits and 90% CI for serum CK (u/L, 37°C) in male and female athletes &amp; non-athletes</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Male athletes</td>
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<tr>
<td>Male non-athletes</td>
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<tr>
<td>Female athletes</td>
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<tr>
<td>Female non-athletes</td>
</tr>
</tbody>
</table>
**Common signs & Symptoms of ER:** classic triad: muscle pain, weakness in affected muscles, tea colored urine. Symptoms often precipitated by strenuous exercise or exertion 24-48 hours prior to presentation

- “Novel” exercise & eccentric exercise associated with increased muscle damage

**Diagnosis:** made by serum creatine kinase (CK) and urinalysis: CK = or > 5 times normal (Reha ’89), > 10 times normal (Am College Cardiology), or a urine dipstick (+) for blood with no red blood cells upon microscopic assessment. Urine or serum myoglobin more definitive when available. Myoglobin will not appear until 0.5-1.5 mg/dl. "Classic" finding of reddish brown / tea colored urine is not seen (reddish brown or tea colored urine) until serum levels of myoglobin are 100 mg/dl. CK levels begin to rise 2-12 hours after injury, peak in 1-3 days and then decline in 3-5 days. **Elevation of CPK has not been shown to correlate with severity of associated renal failure.**

**Treatment:** hospitalization with aggressive intravenous fluid (IVF) and correction / prevention of electrolyte abnormalities if renal function is abnormal and/or as indicated. Can sometimes treat with oral rehydration if renal function normal and serial monitoring available.

Treatment rarely includes alkalisation of urine (sodium bicarbonate 1 ampule / 1 L NS or 2-3 ampules in 1 L D5W administered at 100 ml/hr. Urine pH maintained at > 6.5, with plasma pH between 7.4-7.45), treatment of hyperkalemia (most severe in the first 12-36 hours after muscle injury), and hypocalcemia. IV calcium indicated only for tetany or EKG changes secondary to hypocalcemia or hyperkalemia.

**Prognosis:** overall very good, full recovery of renal function common.

**Special Contributing Factors to Consider:**

**Concerns related to Supplements?** (Elsayed '11, Dehoney '09, Mazokopakes '08, Anon '08, Burke '07, Stahl '06)

- Thermogenesis; increased metabolic rate
- Stimulants; increase blood pressure, heart rate, stress to CV system, false sense of "energy"
- Combinations; synephrine/caffeine have potential additive effects
- Contaminants or adulterants; steroids, stimulants, prescription drugs

**Concern for specific supplements,** such as DMMA (dimethylamlyamine) that have been associated with deaths. DMAA marketed for use in bodybuilding and weight loss supplements.

**Sickle Cell Trait**

In NCAA Football, high incidence of sudden death events associated with SCT (+) athletes April 2010; NCAA adopted policy to require Div I schools to test for presence of SCT.

3 million people in US and 300 million people in world have SCT (Jordan '11, O'Connor '12)
In US: 1/14 African Americans, 1/183 Hispanic/Latino, 1/625 Whites vs In West Africa, 4/10 have SCT
Increasing evidence for association between SCT and hematuria, renal papillary necrosis, splenic infarction, hypoesthenuria, exertional rhabdomyolysis and exercise related sudden death (Tsaras '09)

**SCT and SCD in athletes; what data do we have?**

- **Military:** > 450,000 military recruits btwn 177-1981; 30 X risk of sudden death (RR 30 (11-84)) (Kark '87)
- **NCAA:** Div I Af Am FB players (+) SCT 37 X risk sudden death c/w those without SCT (RR of 1:805) (Harmon '12)
- Increased sudden death in SCT (+) due to both Exertional Heat related Illness (due to SCD, acute renal failure) (Kark '94)
- Exercise results in a decrease in rbc deformability more so in SCT (+) vs those SCT (-). Adequate hydration can normalize the hematologic abnormalities that occur w/ SCT (Connes '08)
- "Heat is no more a trigger for exertional sickling than is altitude, asthma, heedless valor, or a reckless coach" (Eichner ER '10)
- Educational efforts re: SCT in athletes. Decrease training, allow athletes to set own intensity/training, adequate hydration. Attention to risk factors (eg asthma, altitude, dehydration, illness)

**Return to Play;** No clear consensus on RTP after episode of ER (Eichner '08, O'Connor '08)

- At minimum, renal function should be normal, and athlete should be clinically normal
- CK level at which it is “safe” to allow RTP is less clear, especially given variability of individual CK levels

**Return to Play for the Low Risk Warrior Athlete** (O'Connor '08)

<table>
<thead>
<tr>
<th>Phase I</th>
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<tbody>
<tr>
<td>Rest for 72 hr &amp; encourage oral hydration</td>
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<tr>
<td>Sleep 8 h consecutively, nightly</td>
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<tr>
<td>Remain in thermally controlled environment if ER occurred in association with heat injury</td>
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<tr>
<td>Follow up in 72 hr for repeat CK &amp; UA</td>
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<tr>
<td>When CK is &lt; 5 times upper limit normal, begin Phase II. Otherwise remain and return Q 72 hrs w/ repeat CK until &lt; 5 times normal and U/A normal</td>
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<tr>
<td>If CK remains &gt; or = to 5 times upper limit normal and/or UA persistently abnml for 2 wk, refer to expert</td>
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**Phase II**

- Begin light activities, no strenuous physical activities
- Physical activities at own pace and distance
- Follow up with care provider in 1 wk
- If no return of clinical sx, then begin Phase III. Otherwise remain in Phase II and return at 1 wk intervals. May progress to Phase III when no significant muscle weakness, swelling, pain or soreness. If muscle pain persists without objective findings beyond 4 wk, consider specialty evaluation to include psychiatry.

**Phase III**

- Gradually return to regular sporting activities and physical training
- Follow up with care provider as needed


- Delayed clinical recovery (> 1 wk when activity restricted)
- Persistent CK elevation despite 4 wks rest
  - ER complicated by acute renal failure of any degree
- Muscle injury after low to moderate workload
- Personal or FH for
  - Rhabdomyolysis
  - Malignant hyperthermia
  - Recurrent muscle cramps/severe muscle pain that interferes w daily activities
- Sickle cell trait
- Significant heat injury
- Complicated by drug or supplement use (e.g., statin, ephedra, steroids, creatine)
- CPK peak > 100,000 U/L

**Prevention:**
- **Avoid doing too much, too soon of an exercise that is new.**
- Consider functional & fitness screening to risk stratify those at risk for ER.
- Avoid dehydration, heat stress, encourage rest periods and monitoring for overtraining.
- Follow recommendations for Extreme Conditioning Programs that foster a slow progressive buildup and avoid over-exertion and fatigue (Bergeron, ACSM ’11). **“An effective and safe conditioning regimen must consist of incremental, progressive introduction of exercises and workloads based on fitness and specific conditioning needs and limitations of the individual”**
- Consider SCT testing in high risk groups

**References**


Brown TP: Exertional Rhabdomyolysis: Early recognition is key. Phys & Sportsmed 2004


