Clinical Review of Exertional Rhabdomyolysis for the Chiropractic Sports Physician

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Introduction

Dr. James Geiselman

- Assistant Professor of Allied Health at Graceland University
- Doctor of Chiropractic - Logan University
- Master of Science in Nutrition and Human Performance - Logan University
- Diplomate of the American Clinical Board of Nutrition (DACBN)
- Certified Chiropractic Sports Physician (CCSP)
- International Certificate in Sports Chiropractic (ICSC)
- Nationally Registered Emergency Medical Technician (NREMT)
- IL Emergency Medical Technician – Paramedic (EMT-P)

Learning Objectives

At the end of this presentation participants will be able to:

- Define exertional rhabdomyolysis (ER)
- Explain clinical presentation for ER
  - Describe the signs and symptoms of ER
  - Compare the signs and symptoms of general rhabdomyolysis and ER
- List key athletic events with a higher risk of athletes experiencing ER
- Identify key laboratory testing components associated with the diagnosis of ER
- Interpret bio markers associated with the diagnosis of ER
- Apply the knowledge learned to provide treatment and management to patients with ER

Background Information

Rhabdomyolysis

- Rhabdomyolysis is an umbrella term used to describe the result of rapid destruction and breakdown of skeletal muscle tissue resulting in damaged muscles cells leaking their contents into the bloodstream[3,5]
- Rhabdomyolysis is a common and potentially fatal condition encountered by:[34]
  - Athletic Trainers
  - Coaches
  - Primary Care Physicians
  - Sports Medicine Physicians
- Sports reporting cases of ER include:[15,35]
  - American football
  - Swimming
  - Bodybuilding
  - Running
  - Wrestling

Rhabdomyolysis

- When the components of striated muscle such as the myofibrils and sarcolemma are damaged[2,3,5,19,26,27,30,34], cellular components including:
  - Creatine Kinase (CK/CPK)[2,5,6,20,28,19,27,34]
  - Lactate Dehydrogenase (LDH)[6,28,34]
  - Aspartate Transaminase (AST)[6,28]
  - Alanine Transaminase (ALT)[6,28]
  - Calcium[20,26]
  - Potassium[5,20,26,27,34]
  - Myoglobin[5,6]
  - Phsphate[20]
  - Electrolytes[5]
  - Organic Acids[26]
  - are released in the surrounding plasma and extracellular space[19,30]
- Myoglobin is particularly toxic to the renal tubules[3]

Rhabdomyolysis

- Exertional (exercise induced) Rhabdomyolysis (ER) is often diagnosed as rhabdomyolysis in the emergency setting though this diagnosis may not be interchangeable in the presence of comparing the general population with the athletic population.
- Debate revolves around the diagnosis of ER as there is relatively little consensus within the fields of emergency medicine and sport medicine on the overall associated clinical presentation and laboratory findings which may be causing a general misunderstanding regarding appropriate diagnosis[26]
- ER is thought of as an abnormal condition
  - Literature has shown that often times, this condition is the result of normal physiological responses in the body as the result of tissue repair and adaptations to physical activity[6,26,34]

Rhabdomyolysis

- Benign, or physiological, ER may resemble delayed onset muscle soreness (DOMS)
- This becomes clinically significant when accompanied by other morphologies including:[6]
  - Severe Muscle Pain
  - Swelling
  - Myoglobinuria
- It has been theorized that DOMS is a mild form of rhabdomyolysis as it is an indicator of muscle damage post exercise[29,35]

Causes

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Potential Causes of Rhabdomyolysis

- Several causes of rhabdomyolysis have been reported[5]
  - Trauma[20]
    - Crush syndrome[5,35]
    - Abuse
    - Electrical Shock
  - Vascular Obstruction
    - Ischemia[5,20,35]
    - Infections[20]
    - Immobility (Clots)[20]
    - Embolism
  - Seizures or Cramping
  - Environmental Related Emergencies[20]
    - Heatstroke
    - Hyperthermia[5,35]
    - Hypothermia[5,35]
  - Excessive Physical Activity and Strain[5,35]
  - Unaccustomed or New Physical Exercise (exacerbated by dehydration)
  - Drugs[20]
  - Toxins[20]
  - Endocrine Disorders[20]

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Potential Causes of Exertional Rhabdomyolysis

- Prolonged repetitive exercise that involves a heavy eccentric component causing increased muscle damage to the muscle fibers and z bands[2,3,6,23,26,30,34] particularly in extreme heat and humidity[2, 3,5,6,29,30,34] have been directly linked to the development of ER.

Potential Causes of Exertional Rhabdomyolysis

- Other major factors that have been linked to the development of ER include:
  - Deconditioning[2,5,29,30]
  - Extreme CrossFit training[3,5]
  - Dehydration[2,5,6,28,29,34]
  - Electrolyte imbalances[5,29]
  - Nutrition and diet[2,30]
  - Drugs including diuretics and statins[19,29,34]
  - Nonsteroidal anti-inflammatory drugs (NSAIDS)[6]
  - Recreational drugs[34]
  - Dietary supplements[30,34]
  - Immobility[3]
  - High doses of caffeine[34]

Risk Factors and Epidemiology

Risk Factors

- Numerous studies have linked rhabdomyolysis and ER to a variety of sports and professions including:
  - Law enforcement trainees[2,6,27]
  - Firefighting traininees[2,3,6, 26,27]
  - Military cadets[2,3,5,6,26,27]
  - Athletes in
    - Wrestling[2]
    - Football[2,5,34]
    - Swimming[34]
    - Long-distance running[5]
  - Vigorous Exercise / High Intensity Resistance Training[5,23]
  - Physical Education class[26]

Risk Factors

- Other factors[19,29,30]
  - Sex
    - Male vs Female
  - Ethnicity
    - African American > Caucasian and South Asian[20,21]
      - Linked to Sickle Cell Trait[5,6,19,34]

Epidemiology

- Though relatively uncommon, ER is potentially fatal[35]
- Every year, there are approximately 22.2 - 29.9 cases per 100,000 patients each year[5,20,35]
- Other studies report roughly 26,000 cases each year[20]
- Difficult to truly determine frequency of ER as many mild cases go unrecognized and unreported[20]
- ER tends to reoccur at a rate of 0.08% to 11%
  - may be higher in patients with genetic or muscular disorders[20]

Complications of Rhabdomyolysis

Complications

- Rhabdomyolysis and ER are concerning as they have been associated with a variety of complications including:
  - Metabolic acidosis[26]
  - Disseminated intravascular coagulation (DIC)[5,19,20]
  - Hypocalcemia[26]
  - Hyperkalemia[5,19,26]
  - Arrythmias[20,26,34,35]
  - Sickling collapse[5]
  - Compartment syndrome[2,5,19,26,30,34]
  - Acute renal failure[2,5,19,20,30,34]
  - End Organ Failure[20]
  - Cardiac arrest[2]
  - Death[2,26,30,35]

Renal Consequences

- Renal injury is reported in up to 50% of cases[20]
- Myoglobin is particularly toxic to the renal tubules
  - concern because it may precipitate in the renal tubules, causing acute renal failure[14]
- Acute Renal Failure is rare[5]
  - 3-7% of ER cases progress to ARF
    - usually with contributing factors such as dehydration, heat stress, trauma, or underlying disease such as sickle cell trait.
  - May occur 1 to 2 days after initial muscle damage
  - Renal tubular obstruction occurs secondary to precipitation of uric acid and myoglobin
  - Decreased renal perfusion is further compounded by dehydrations, heat stress, or hypotension
- Other studies have reported that elevated level of serum CPK/myoglobin as the result of upper-extremity exertion, did not usually lead to ARF[14]

Special Note:

- While acute renal failure is one of the most well-known and concerning complications of rhabdomyolysis, acute renal failure in ER patients is particularly rare and when it does occur, full recovery is nearly universal[19,20]

Compartment Syndrome

- Associated muscle swelling may exert pressure on peripheral nerves, resulting in neuronal ischemia and causing paresthesia or paralysis

- Nerve injury is often proximal, and multiple nerves may be involved in the same extremity[5]
  - ex: 14 high school American football players experienced rhabdomyolysis during summer training after performing an unaccustomed exercise bout. Push-ups and chair dips were performed continuously with almost no rest for intervals of 30 seconds each and then repeated until failure for many athletes. The consequences of this exercise bout resulted in hospitalization of 14 players, 3 of whom required an emergency fasciotomy of their triceps brachii.

ECG Changes

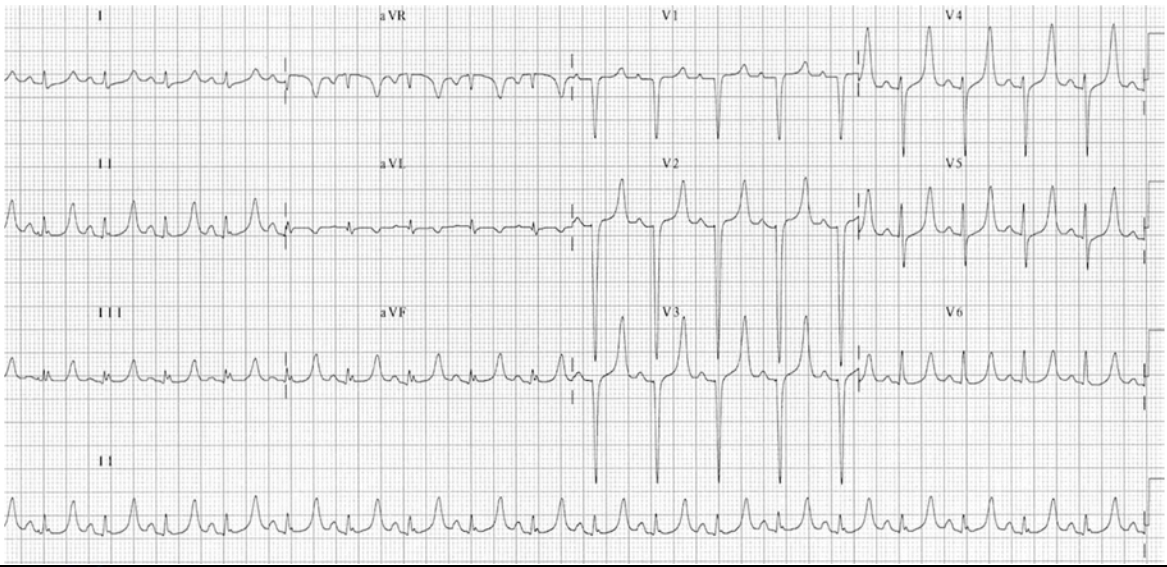
- Characteristics of hyperkalemia on an ECG:
  - Peaked T waves
  - P waves that widen and flatten
  - Prolonged PR interval
  - May lead to bradyarrhythmias
  - QRS abnormalities
- As hyperkalemia worsens, it can lead to:
  - Ventricular Fibrillation
  - PEA
  - Asystole
- Serum K+ levels do not always correlate with ECG changes. Sudden cardiac arrest is possible in these patients[38]

HyperKalemia

- Life-threatening electrolyte imbalances can results from ER[5]
  - 98% of K+ is found in the intracellular space
  - 60%-70% of the total cellular mass of the human body consists of skeletal muscle cells
    - Even acute necrosis of only 100 grams of muscle mass could potentially increase serum measurability.

Serum potassium	Typical ECG appearance	Possible ECG abnormalities
Mild (5.5-6.5 mEq/L)		Peaked T waves Prolonged PR segment
Moderate (6.5-8.0 mEq/L)		Loss of P wave Prolonged QRS complex ST-segment elevation Ectopic beats and escape rhythms
Severe (>8.0 mEq/L)		Progressive widening of QRS complex Sine wave Ventricular fibrillation Asystole Axis deviations Bundle branch blocks Fascicular blocks

Hyperkalemia

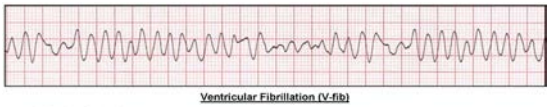


Sudden Cardiac Arrest

- Incidence are estimated to occur 1 per 50,000 to 1 per 300,000 patients[38]
- Typical victim:
  - Young
  - Apparently healthy
- For many, no cause is ever found
- Theory
  - Since athletes are prone to muscle injury due to exercise, resulting rhabdomyolysis may lead to electrolyte imbalances (due to the release of muscle cell contents, including potassium K+)[38]
  - This efflux of potassium may lead to electrical abnormalities of the heart[38]

Most Serious Arrhythmias

Ventricular Fibrillation[36]

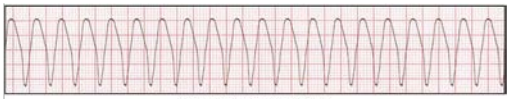


Ventricular Fibrillation (V-fib)

Rhythm: Chaotic
Rate: Chaotic
P Waves: Absent
P-R Interval: Absent
QRS: Absent

Clinical Significance: Ventricular fibrillation is lethal with no cardiac output. Defibrillate with an initial unsynchronized dose of 360 joules monophasic or 120-200 joules biphasic. 1mg Ephinephrine 1:10,000 is the drug of choice given every 3-5 minutes.

Ventricular Tachycardia[37]

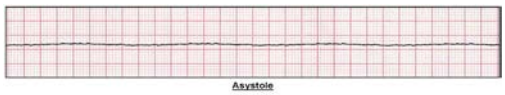


Ventricular Tachycardia (V-tach)

Rhythm: Regular (Can be slightly irregular)
Rate: 200 bpm (Typically between 100-250)
P Waves: Absent
P-R Interval: Absent
QRS: Wide, 0.32 sec (usually wide and bizarre)

Clinical Significance: Ventricular tachycardia severely compromises cardiac output and coronary artery perfusion. V-tach May be perfusing or non-perfusing. If there is a pulse and patient is stable, then Procainamide or Amiodarone may be administered. If unstable with a pulse, then synchronized cardioversion is needed. If pulseless, then defibrillate with an initial unsynchronized dose of 360 joules monophasic or 120-200 joules biphasic.

Asystole[1]

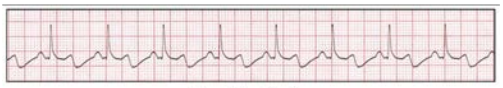


Asystole

Rhythm: None
Rate: None
P Waves: Absent
P-R Interval: Absent
QRS: Absent

Clinical Significance: Asystole is cardiac arrest with no electrical activity. Treat with high quality CPR and 1mg Epinephrine 1:10,000 given every 3-5 minutes. Try to correct underlying causes such as H's and T's.

PEA[25]



Normal Sinus Rhythm

Rhythm: Regular
Rate: 80 bpm (normal range= 60-100 bpm)
P Waves: Upright and regular
P-R Interval: 0.16 sec (normal range= 0.12-0.20), one P wave for each QRS
QRS: 0.08 sec (normal range= 0.04-0.12)

Clinical Significance: Unless the patient has no pulse or other serious signs or symptoms, there is no significance to this cardiac rhythm.

Clinical Presentation

Clinical Presentation

- In severe cases of rhabdomyolysis, general symptoms may include:[5]
  - Fatigue
  - General malaise or ill feeling
  - Fever
  - Nausea and vomiting
  - Electrolyte disturbances
  - Tachycardia
  - Seizures

Clinical Presentation

- Muscle pain is often described as being intense and severe during active and passive ROM[2,6,19,26,27,30,34]
- Muscle weakness and generalized fatigue is often prevalent after prolonged and repetitive exercises especially in those who are unfamiliar with exertional levels or new to activity[6,26,27]
- The presence of myoglobinuria is often described as being dark, tea, or cola-colored

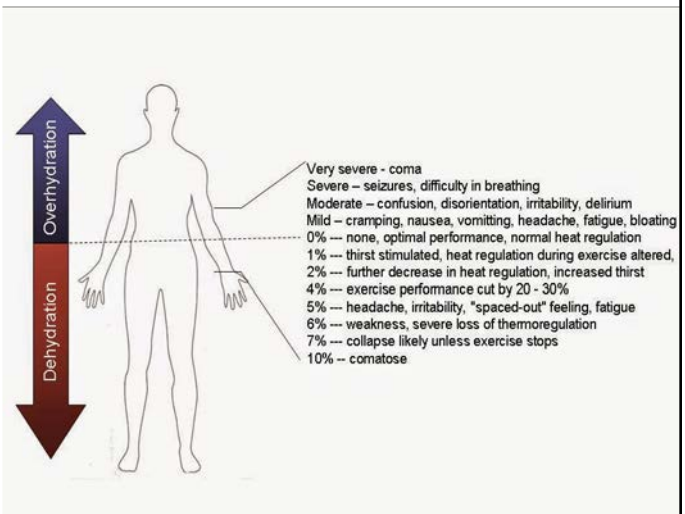
Clinical Pearls

- The 3 primary **SYMPTOMS** are as follows:
  1. Muscle Pain[2,6,19,26,27,30,34]
  2. Muscle Swelling[2,19,26,30]
  3. Myoglobinuria[2,6,26,27,30,34]
- The 3 primary **DIAGNOSTIC CRITERIA** are as follows:[5]
  1. Dark, tea- or cola-colored urine (myoglobinuria)
     a. Appearing 12 to 24 hours after initial muscle damage
  2. Myalgia
     a. Muscle pain, tenderness, weakness, and edema
  3. Elevated serum muscle enzymes
     a. Increased CK for 24 to 48 hours then gradual decline

Hydration

Hydration Status

- Hydration is a foundational component for any athlete with ER[35]
- Factoring in an athlete's sport, environment, and nutritional goals, can aid in the diagnosis of ER



Hydration Levels

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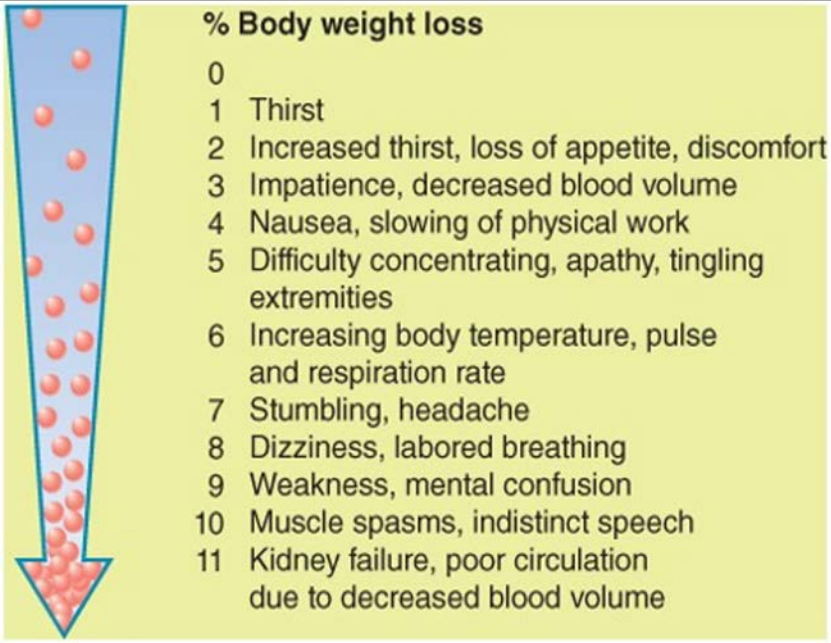
Dehydration Consequences



% Body weight loss	
0	
1	Thirst
2	Increased thirst, loss of appetite, discomfort
3	Impatience, decreased blood volume
4	Nausea, slowing of physical work
5	Difficulty concentrating, apathy, tingling extremities
6	Increasing body temperature, pulse and respiration rate
7	Stumbling, headache
8	Dizziness, labored breathing
9	Weakness, mental confusion
10	Muscle spasms, indistinct speech
11	Kidney failure, poor circulation due to decreased blood volume

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Dehydration

- Exercise-related renal impairment usually occurs as a result of dehydration[3]
- Exercise results in fluid losses of 1-2 L/h, particularly in hot conditions (ie: wrestling rooms, 2-a-days Football)[3]
- Aggressive fluid replacement can cause hyponatremia[3]
- Most commonly, acute renal failure with associated hyperkalemia may ensue[3]

Clinical Dehydration

- Elevation of key ER biomarkers such as:
  - Na+
  - BUN
  - P_{osm}
  - AST
  - CK
  - LDH
  - Have been noted in the dehydrated athletes with significant statistical correlations of Na+ and BUN in relation to dehydration and skeletal muscle damage[28]
- NOTE: Dehydration may prevent athletes from clearing myoglobin and other toxic substances[29]

Differential Diagnosis

Differential Diagnosis

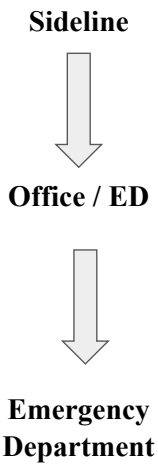
- Without a high index of suspicion, it is common to miss cases of rhabdomyolysis[5]
  - Primarily due to the general symptoms an athlete will present with
    - Muscular pain
    - Swelling
    - Tenderness
    - In some cases, these symptoms are not prominent and may even be absent[5]
- If ER is suspected, immediate referral to higher-level care for definitive diagnosis is required
  - Diagnosis is confirmed with laboratory tests evaluating serum levels of CK and urine myoglobin[5]
- Other causes of muscle pain and weakness besides ER should be considered in the appropriate clinical and sideline setting[5]

Differential Diagnosis

- Muscle pain and weakness differential diagnosis may include:[5]
  - Acute myopathies
  - Periodic paralysis
  - Polymyositis or dermatomyositis
  - Guillain-Barre syndrome
  - Muscle Strain
  - Discogenic involvement
  - Etc.
- In more serious cases, it is crucial that you rule out the 3 most common non-traumatic causes of sudden exertional collapse in healthy people[5]
  1. Cardiac condition
  2. Heatstroke
  3. Asthma
- Signs of serious causes of exercise related collapse include:
  - Altered mental status (AVPU)
  - Systolic BP less than 100 mmHg
  - Heart rate greater than 100 bpm

Additional Keys to Aiding in Diagnosis

- Dark urine, without other symptoms, may not indicate ER but rather dehydration or other causes of hematuria[5]
- Acute CK elevation at least 5 x the upper limit of normal is conservatively used to aid in diagnosis[5,8]
  - This low threshold has been shown to have high sensitivity, but low specificity[8]
- Criteria that indicate hospitalization is necessary include the following[5]
  - Highly increased CK activity
  - Decreased creatinine clearance
  - Elevated serum creatinine
  - Myoglobinuria
  - Metabolic abnormalities
  - Signs of compartment syndrome



Confirmed Diagnosis

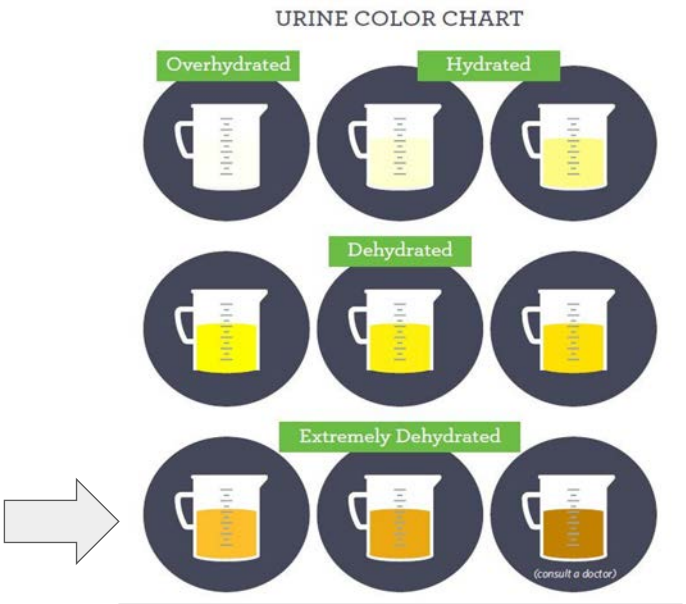
- History + Exam Finding
  - History
    - Risk Factors
  - Examination Findings
    - Tenderness of the affected muscle groups
    - Possible hypovolemia

- Laboratory findings in the hospital setting often include:
  - CBC
  - CMP (K+, Na, Cl-, glucose, creatinine, CO2, Blood Urea Nitrogen)
  - Creatine Kinase (CK) level >1000 IU/L (5x UL)

- Urine dipstick can test positive for myoglobin without microscopic evidence of blood

- **Interesting note**: ICD-10 codes should not be used unless absolute as to not hinder future research[8]

Early Detection



Sideline Recognition

National Athletic Training Association (NATA) has identified four factors that may lead to exertional rhabdomyolysis[5]

1. Performing 2 - 3 minutes of all-out, vigorous, exhaustive, or maximal physical exertion (usually during training and conditioning)
2. Sprinting short distances (800 to 1,600 meters) without adequate rest periods
3. Vigorously exercising the first day of preseason or early in the season without adequate acclimatization
4. Sprinting at the end of practice such as gassers or suicide sprints while exhausted or fatigued

NATA[31]

1. Transition periods are particularly vulnerable times for athletes and demand careful attention to progression in volume, intensity, mode and duration of activity. Examples of transition periods:

- *a. Athletes new to the program.*
- *b. Athletes returning after an injury or illness.*
- *c. Any delayed participation relative to the team schedule.*
- *d. Resumption of training after an academic break (e.g., winter, spring, summer).*

2. All strength and conditioning workouts should be exercise-based, scientifically sound and physiologically representative of the sport and its performance requirements.

3. Conditioning programs should begin with a work-to-rest ratio of 1-to-4.

4. The first four days of transition periods should be separate-day workouts, and all workouts:

- *a. Should be documented in writing.*
- *b. Should be intentional.*
- *c. Should increase progressively in the volume, intensity, mode and duration of physical activity.*

5. All strength and conditioning workouts:

- *a. Should be documented in writing.*
- *b. Should reflect the progression, technique, and intentional increase in the volume, intensity, mode and duration of the physical activity.*
- *c. Should be available for review by athletics department staff.*

Diagnostics

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Typical Diagnostic Workup

- Electrocardiogram[20]
- Urine Analysis (Dipstick)[20]
- Blood[20]
  - CBC
  - Electrolytes
  - Renal and Liver Function
  - CK
  - Uric Acid

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Common ECG Changes

Hypercalcemia
- -shortened QT interval
- -increased QRS
- -bradycardia

Hyperkalemia
- -peaked T-waves (chest leads)
- -P-waves may become wide
- -prolonged PR interval
- -wide QRS (severe cases)

Hypermagnesemia
- -rare
- -may lead to AV blocks and Asystole

Hypernatremia
- -No ECG changes

Hypocalcemia
- -lengthened QT interval
- -shortened QRS

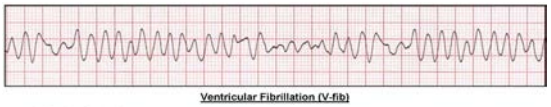
Hypokalemia
- -wider T-waves / lower amplitude
- -ST depression w/ inverted T-waves
- -amplification of P-waves
- -U-waves may appear

Hypomagnesemia
- -SVT or Ventricular tachyarrhythmias

Hyponatremia
- -No ECG changes

Most Serious Arrhythmias

Ventricular Fibrillation[36]



Ventricular Fibrillation (V-fib)

Rhythm: Chaotic
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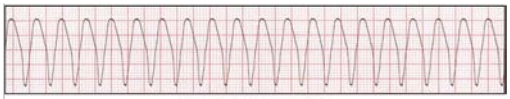
Clinical Significance: Ventricular fibrillation is lethal with no cardiac output. Defibrillate with an initial unsynchronized dose of 360 joules monophasic or 120-200 joules biphasic. 1mg Ephinephrine 1:10,000 is the drug of choice given every 3-5 minutes.

Ventricular Tachycardia[37]



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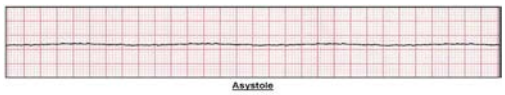
Clinical Significance: Ventricular tachycardia severely compromises cardiac output and coronary artery perfusion. V-tach May be perfusing or non-perfusing. If there is a pulse and patient is stable, then Procainamide or Amiodarone may be administered. If unstable with a pulse, then synchronized cardioversion is needed. If pulseless, then defibrillate with an initial unsynchronized dose of 360 joules monophasic or 120-200 joules biphasic.

Asystole[1]



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Clinical Significance: Asystole is cardiac arrest with no electrical activity. Treat with high quality CPR and 1mg Epinephrine 1:10,000 given every 3-5 minutes. Try to correct underlying causes such as H's and T's.

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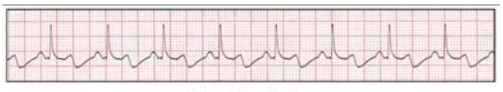

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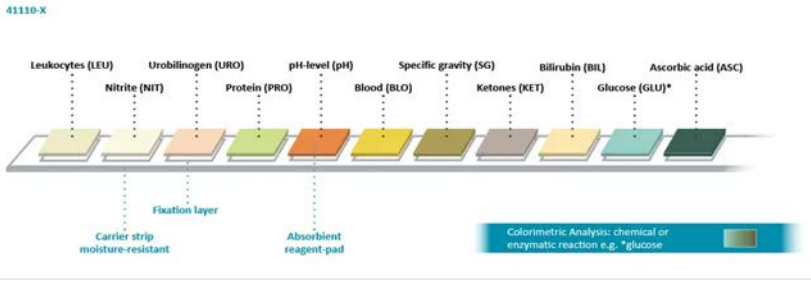
QRS: 0.08 sec (normal range= 0.04-0.12)

Clinical Significance: Unless the patient has no pulse or other serious signs or symptoms, there is no significance to this cardiac rhythm.

Urine Analysis (Dipstick)

- Components of the Urine Dipstick w/normal[24]
  - specific gravity – 1.001-1.035
  - pH – 4.6-8.0
  - Protein - negative
  - Glucose - negative
  - Ketone - negative
  - Bilirubin - negative
  - Blood - negative
  - Nitrite - negative
  - Leukocyte - negative



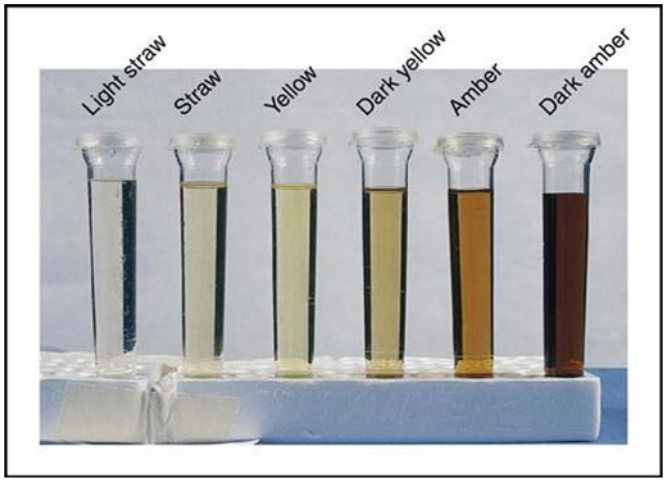
Myoglobinuria

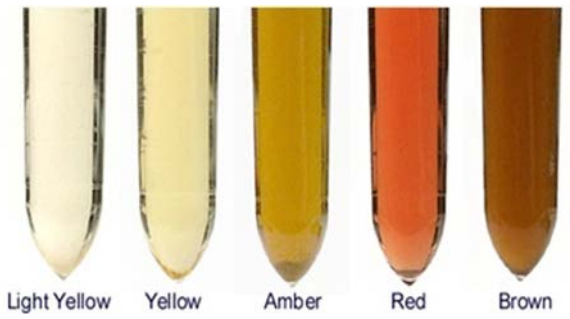
- Most important consequence of significant muscle breakdown in ER[5]
- Develops once more than 100 grams of skeletal muscle has been damaged[5]
- Myoglobin will spill over into the urine after plasma concentrations reach more than 1.5 mg/dL
  - This results the typical reddish-brown discoloration when the urine myoglobin level is more than 100 mg/dL[5]
- Myoglobinuria may be detected with a urine dipstick or macroscopically as reddish-brown urine in severe cases of ER[5]

Myoglobinuria

- Serum levels of myoglobin rise within 1 to 6 hours and peak in 8 to 12 hours
  - Levels begin returning to normal within 24 hours after the onset of the injury[5]
- If serum myoglobin exceeds 0.3 mg/L, it becomes detectable with a urine dipstick
  - Urine dipsticks are inexpensive and sensitive test[5]
    - Ideal for sideline and office settings
- Major drawback is you cannot distinguish between hemoglobin, myoglobin, or hemoglobin-rich red blood cells
  - Urine dipsticks detect heme-rich molecules[5]

Urine Samples





Blood Test

- Complete Blood Count (CBC)
- Comprehensive Metabolic Panel (CMP)
- Creatine Kinase (CK/CPK) (total, serum, or plasma)
  - NOT to be confused with a CK-MB

CBC Components

- White blood cell count (WBC or Leukocyte count)
- WBC differential count
- Red blood cell count (RBC or erythrocyte count)
- Hematocrit (Hct)
- Hemoglobin (Hbg)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Red cell distribution width (RDW)
- Platelet count
- Mean platelet volume (MPV)

CMP Components

- Glucose
- Calcium
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Blood Urea Nitrogen (BUN)
- Creative
- Albumin
- Total Protein
- Alkaline Phophatase (ALP)
- Alanine Aminotransferate (ALT)
- Aspartate Aminotransferase (AST)
- Bilirubin

Additional Findings

- Creatine Kinase (CK) is the Gold Standard for diagnosis rhabdomyolysis[8]
- However, four other enzymes have been found to be potentially elevated in rhabdomyolysis[22,23]
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Lactate dehydrogenase
  - Aldolase

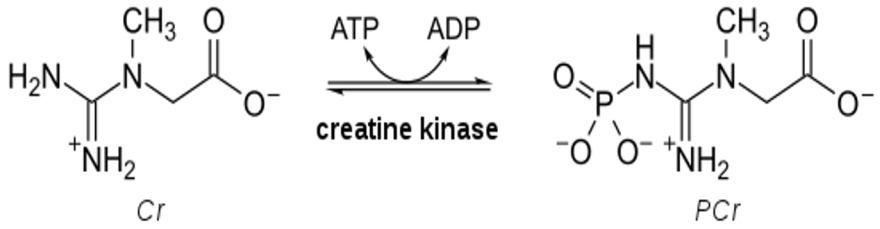
Other Laboratory Findings

- If rhabdomyolysis is suspected, the serum levels of the following should be evaluated and may be elevated:[11]
  - Potassium
  - Phosphate
  - Uric acid
  - Creatine
  - Lactate dehydrogenase
- While the following may be decreased
  - Calcium
  - pH

Creatine Kinase

What is CK?

- Creatine kinase is an enzyme that catalyzes the reaction transferring phosphate from creatine phosphate to adenosine diphosphate to make ATP.
- ATP-CR Energy System



Creatine Kinase (CK/CPK)

- Enzyme which catalyzes the interconversion of creatine and phosphocreatine (PCr)[24]
- Skeletal muscle, myocardium, and brain are rich in the enzyme
- CK is released when there is tissue damage
  - increased in the following:
    - MI
    - Myocarditis
    - Rhabdomyolysis
    - Muscle trauma
    - Severe muscle exertion
    - Hypothyroidism
    - Surgery
    - Tetanus
    - Alcoholism
    - Statins

CK

- An elevated serum CK is the most sensitive and reliable indicator of muscle injury and constitutes the diagnostic hallmark of ER[5,8]
- CK levels are strongly affected by race, sex, and physical activity[22]
- In general, CK levels begin to rise approximately 2 to 12 hours after the onset of muscle injury, peak within 24 to 72 hours, and then gradually decline (over a 5 to 10 day period)[20]
- Training for sports of competition tends to have a profound effect on serum CK, and athletes have higher CK values that non-athletes[5,23,24]
- Many cases of exertional rhabdomyolysis are subclinical
  - Some cases are only detected by elevated serum CK level

CK Levels to Diagnosis ER

- CK/CPK is one of the most commonly used biomarkers in the diagnosis of rhabdomyolysis
  - CK/CPK levels ranging from 5 times to 50 times upper normal limits have been proposed in the literature[8,34]
- CK/CPK levels of 5-10 times higher than normal upper limits is the primary diagnostic laboratory sign of rhabdomyolysis[14]
- In the presence of a natural history, serum CK >25,000 U/L is likely benign in ER patients[5]
- It is not unusual to see CK levels up to 100,000 IU/L[5]
- When ARF is present in patients with ER, serum CK levels may exceed 15,000 U/L
  - Values have even been documented at levels of 3,000,000 U/L[5]

The Problem with CK

- No standard CPK level is diagnostic for rhabdomyolysis[5,14]
  - Standard reference ranges by most labs are too low and can often lead to overdiagnosis[22]
- No definitive algorithm exists that predicts when rhabdomyolysis will have detrimental effects[14]
- Clinically, ER is often diagnosed with elevation of serum CK/CPK to more than 5x UL[5,8]
- 5x upper limits of CK/CPK are often mentioned as being a conservative range for diagnosis[8,19,26]
- CK levels more than 10x the UL were commonly found in people who were asymptomatic, and this is believed to be the value with diagnostic significant[5,19,27]

The Problem Continued

- Other more recently proposed guidelines suggest a diagnosis of ER should be made only when the serum CK is more than 50 x the UL[5]
- With no definitive pathological value for CK/CPK, healthcare providers should be aware that levels of 20x the upper limit may be seen in those performing repetitive and strenuous exercise[19]
- Only CK/CPK values over 5,000 U/L should be concern for renal failure[21]
- Other sources site levels of >10,000 U/L as being the diagnostic threshold for ER[30]

CK Values in ER Patients in the Literature

- Documented cases of CK/CPK laboratory values in excess of[6]
  - 130,000 IU/L in an 18-year-old football place kicker
  - 146,000 IU/L in a 16-year-old male following two days of practice at wrestling camp
  - 244,006 IU/L in a 12-year-old male after performing 250 squat jumps in a physical education class
- Evidence exists that CK/CPK values can range from 2000 IU/L to >10,000 IU/L following 50 maximal eccentric contractions of the elbow flexors[29]
- Knowing when an athlete has moved from a physiological response to a pathological response is difficult to assess and manage without clinical diagnostic testing[6,29]
  - Expected elevation for CK/CPK may explain why team physicians recommended intravenous hydration for athletes with laboratory values >3,000 U/L and hospitalization for athletes over 10,000 U/L[27]

Re-evaluating CK Criteria

- Current laboratory ranges for CK/CPK levels fail to take into account:[21,27]
  - Gender
  - Ethnicity
  - Activity level
- This leaves physicians to use the same laboratory ranges for athletes, as they do for the general population likely leading to incorrect and misguided diagnosis[21,27]
- Athletes have higher CK values than non-athletes which is why comparing values of athletes to the normal values established in non-athletes is not beneficial[24]
- There is a need for sport specific references ranges[21]

Asymptomatic CK Elevation

- In the absence of symptoms, or even minimal non-specific muscle symptoms (cramps, spasms, fatigue), an elevated CK/CPK level is an incidental finding[11,22]
- A more correct diagnosis for elevated CK levels would be "asymptomatic hyper-CK-emia"[22]
- Evidence exists that CK levels rise after exercise or heavy manual labor and may increased to 30 times the UL of normal within 24 hours of strenuous physical activity, then slowly decline over the next 7 days[22]
  - Serum concentrations peak 1-4 days after exercise and remains elevated for several days[24]

Additional Research

Clinical Discussion and Importance

- Prevention is key!
- Future research is needed to:
  - Develop sport specific reference ranges
  - Explore contributing factors associated with developing ER
  - Evaluate a more accurate CK level for both athletes and non-athletes

Study #1: Impact of Dehydration on Elite Wrestlers[18]

- 24 male elite wrestlers
- Pre-competition weight loss practices surveyed
- Biomarkers evaluated
  - Total Creatine Kinase (CK)
  - Lactate Dehydrogenase (LDH)
  - Aspartate Aminotransferase (AST)
  - Alanine Aminotransferase (ALT)
  - C-reactive Protein (C-RP)
  - P_{osm}
- P_{osm} >290 indicated dehydration
- Researchers found serum CK and LDH levels considerably increased after intense exercise
- AST, ALT, CK, and LDH are commonly used to evaluate muscle damage

Results

- CK levels elevated in the weight loss group vs non-weight loss group

Weight Loss Group (Pretest)	Non-weight Loss group (Pretest)
158.27 +/-61.63" "Post-test = 239.60 +/- 115.67	120.11 +/- 20.31" "Post-test = 151.33+/-33.62

Study #2:
Exertional Rhabdomyolysis + D1 Football[32]

- Research hypothesized that a back squat workout would trigger ER in some players
- Serum CK and creatinine values ranged from 96,987 to 331,044 U/L and 1.0 to 3.4 mg/dL, respectively
- Affected players that went to muscle failure, performed extra squats, or did not think they could complete the work out, were more likely to report symptoms than unaffected players
- Protein shakes may have a protective effect and decrease the risk of developing ER
- Risk of ER was increased based on:
  - Perfect body weight lifted
  - Number of sets
  - Time needed to complete 100 back squats
- This was only the third study to report a cluster of ER cases among NCAA DI universities

Study #3:
Exertional Rhabdomyolysis + D1 Swimming[14]

- 7 collegiate NCAA DI Swimmer presented with:
  - Severe pain and swelling in the triceps brachii muscles
  - Severe pain and swelling in the pectoralis muscles
  - Dark-colored urine
- All swimmer claimed to be hydrated and denied drugs, alcohol, or dietary supplements
- Physical examination revealed:
  - Severe tenderness to palpation over the chest and arms
  - Decreased flexion at the elbows
  - Non-pitting, localized swelling of the bilateral upper triceps brachii and pectoralis muscles
- ED referral “Initial creatine phosphate (CPK) values ranging from 14,417 U/L to 157,700 U/L and aspartate aminotransferase (AST) values from 570 to 2356 U/L.”

Study #4:
CK Levels Post 2-A-Days[11]

- Postexercise CK levels may be 5 to 10x normal UL for men and women
- First study to examine CK levels in football players performing high-intensity exercise in a high heat and humidity environment (2-a-days)
- Normal clearance of CK/CPK from the blood is typically 2 to 3 days.
  - Peak levels occur ~18 hours post-injury
- This study did not examine other laboratory findings such as
  - Electrolyte imbalances
  - pH disturbances
  - Creatinine
  - Lactate dehydrogenase
  - Myoglobinuria

Treatment

Sideline Management and Treatment

- Are these the same?

- Sideline Management
  - What are you doing to mitigate risk?
    - Will oral rehydration be enough?
    - How is your patient? The environment? Training variables?

Versus

- Treatment
  - By the time an athlete comes to you, hospital based treatment may be warranted
    - Personal vehicle vs Ambulance?
    - Intravenous rehydration needed?

Treatment Overview

- Mild cases may go undiagnosed and may be managed in an outpatient setting with oral hydration and rest[5]

- Conservative management consisting of rest and rehydration may be adequate[5]

- Clinic and hospital-based treatments are often necessary and entail intravenous rehydration and re-evaluation of laboratory findings before discharge.
  - Majority of healthy patient with ER and w/o comorbidities can usually be treated with oral or IV rehydration, observed in the ED, and then released[5]
  - IV fluid rehydration goal is 300 ml/h (Lactated Ringers (LR) or 0.9% Normal Saline)[20]

- The need for hospitalization and observation may be warranted in severe case
  - This decision is often derived from the physician's intuition and not based on laboratory findings alone[19]
  - With the potential for serious consequences, physicians and other healthcare providers must use appropriate risk-stratification to determine what kind of risks the athlete is under when returning to activity[26]

Sideline Management

- Having a high index of suspicion is key to early treatment
  - Sports such as:
    - Wrestling
    - Football
    - Swimming
    - Running
    - Weightlifting
- Patient history will lead to possible diagnostics
- Myoglobinuria can be easily detected in the clinical and sideline setting with dipstick analysis
  - one of the quickest and most easily accessible methods of testing for ER[6,30]

Definitive Treatment (Emergency Department / Hospital)

- Dipstick UA in the ED is usually positive for the presence of blood, but microscopic analysis reveals no red blood cells[26]
- CK values aid in diagnosis of ER, but one challenge for emergency medicine physicians and sports medicine physicians is determining whether the clinical presentation and laboratory findings are consistent with physiological ER or pathological ER[26]
- Hospital admission may be required[3]
- Aggressive fluid replacement (4-11 L in the first 24 hours) to protect kidney function[3]

Return to Play

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Return to Play

- RTP is based on assessing risk factors[5]
  - This is further complicated by the fact that there are currently no standardized laboratory markers indicating when recovery has been achieved[34]
- Laboratory testing could rely on cellular biomarkers returning to baseline levels as it would demonstrate the ability of the kidneys to function normally and clear these substances from the body[22,34]
- Athlete's physician should be closely consulted and the patient must be closely monitored during the RTP process[5]

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RTP Continued

- Sports medicine physicians and emergency medicine physicians should be familiar with high-risk patients
  - -Sickle-cell disease
  - -Familial history of rhabdomyolysis
  - -History of hyperthermia
  - -Those with recurrent episodes of ER.
- Patients deemed high-risk should be referred for further follow-up examination and potential studies[3,34]
- When prompt diagnosis and treatment is initiated, the prognosis for a full recovery with full return to play is often achievable[2]

CHAMP Guidelines

Phase 1 • Rest for 72 hours and encouragement of oral hydration • 8 hours of sleep nightly • Remain in a thermally controlled environment if the episode of ER was in relation to heat illness • Follow-up after 72 hours with a repeat serum CK level and UA • If the CK has dropped to below 5 times the upper limit of normal and the UA is negative, the athlete can progress to phase 2; if not, reassessment in 72 additional hours is warranted • Should the UA remain abnormal or the CK remain elevated for 2 weeks, expert consultation is recommended
Phase 2 • Begin light activities, no strenuous activity • Physical activity at own pace/distance • Follow-up with a care provider in 1 week • If there is no return of clinical symptoms, the athlete can progress to phase 3; if not, the athlete should remain in phase 2 checking with the health care professional every week for reassessment; if muscle pain persists beyond the fourth week, consider expert evaluation to include psychiatry
Phase 3 • Gradual return to regular sport/physical training • Follow-up with care provider as needed

CHAMP, Consortium for Health and Military Performance; ER, exertional rhabdomyolysis; CK, creatine kinase; UA, urinalysis

CK and Nutrition

- Some research has suggested the consumption of protein shakes may provide possible protection against ER[32]
- Other studies have found that BCAAs can reduce serum levels of CK[32]
- Creatine monohydrate does not appear to play a role in developing ER[29]
- Proper hydration is another key component

Key Points

Red Flags to Remember

- Patients presenting with[5]
  - *Severe muscle pain
  - *Decreased muscle strength
  - *Myoglobinuria
- Common to find
  - *Increased myoglobin
  - *Increased CK levels
- Diagnosis is made with laboratory finding and clinical history

Summary - Takeaways

- Exertional Rhabdomyolysis has a strong eccentric component (muscle-lengthening)[5]
  - -Downhill running
  - -Plyometrics
  - -Negatives (lowering weights)
- Delayed-Onset Muscle Soreness (DOMS) may be suspected after an athletes presents with muscle stiffness following eccentric exercise[5]
  - -This is most likely due to inflammation and sensitization of nociceptors by muscle breakdown products
- Exercise-related muscle injury can be considered a continuum ranging from DOMS to Rhabdomyolysis[5]

Summary - Takeaways

- More than ½ of all patient do not report muscular symptoms[5]
- Myoglobinuria is found in about ½ of the cases, absence does NOT exclude syndrome[5]
- <10% of patient with rhabdomyolysis present with all three conventional symptoms[20]

Summary - Takeaways

- Imperative to understand that exercise can increase CK/CPK levels in the blood
  - -Research is needed to establish sport specific reference ranges necessary for accurate diagnosis[21]
- Bringing awareness to healthcare providers regarding diagnosis, treatment, and management of ER should be of highest importance.
  - -Many athletic training and exercise physiology textbooks do not provide an adequate clinical picture of rhabdomyolysis and/or fail to mention ER[6]
- Healthcare providers working with athletes should educate themselves along with promoting prevention and practice mitigation techniques, via education and dissemination of appropriate information, as this is the ideal treatment strategy for ER.
  - -Teaching athletes the signs and symptoms of ER and the dangers associated with excessive activity is a crucial aspect of clinical practice[2,6]

Case Studies

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Clinical Example #1a - Chief Complaint

24 yo Caucasian M presented to local clinic with vomiting, muscle cramps, and low urine output. Patient received IV fluids (500 mL) at the clinic and was referred to local ED for evaluation.

Thoughts?

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Clinical Example #1a - Additional History

Once in the ED, patient admitted to a 17 lb weight loss in 2 day. Confirmed that he was experiencing muscle cramping, dehydration, and decreased urine output. At the ED, patient was initially unable to urinate, and when he did, it was brown.

What's next?

Clinical Example #1a - Diagnostic Workup

CBC
CMP
CPK
UA

Clinical Example #1a Laboratory Findings

Test	Patient #1a
General Chemistry	
CPK	**460 (0-135 IntUnit/L)**
BUN	**26 (9-20 mg/dL)**
BUN/Creat Ratio	21
AST	45 (17-59 IntUnit/L)
Na+	137 (136-145 mmol/L)
K+	4.7 (3.0-5.5 mmol/L)
Macroscopic Urinalysis	
UA Color	**dark yellow**
UA Protein	100
UA Specific Gravity	**>=1.030**
UA Blood	**trace-lysed (A)**
Microscopic Urinalysis	
UA RBC	0-2
* = CK lab value † = no data available	

Clinical Presentation #1a - Treatment

Patient received:

1. 2 x NS 1,000 mL
2. No activity for 5 days, then gradual RTP

Final Diagnosis:

1. Rhabdomyolysis
2. Dehydration
3. Muscle cramping
4. Low urine output

Clinical Example #1b - C/C and History

RTP - 5 days following ED visit

6 days following initial ED visit (1 day after RTP), patient began experiencing muscle tightness after practice.

7 days following initial ED visit (2 days after RTP), patient's pain increased and the patient had newly developed nausea, vomiting, muscle pain, and flank pain. Was evaluated in the clinic.

In office UA + for protein and bilirubin but - for blood and ketones.

Clinical Example #1b - Diagnostic Workup

CBC
CMP
CPK
UA

Clinical Example #1b Laboratory Findings

Test	Patient #1b
General Chemistry	
CPK	**353 (0-135 IntUnit/L)**
BUN	**25 (9-20 mg/dL)**
BUN/Creat Ratio	17
AST	40 (17-59 IntUnit/L)
Na+	136 (136-145 mmol/L)
K+	4.2 (3.0-5.5 mmol/L)
Macroscopic Urinalysis	
UA Color	**darker**
UA Protein	+
UA Specific Gravity	
UA Blood	**Neg**
Microscopic Urinalysis	
UA RBC	†
* = CK lab value † = no data available	

Clinical Example #1b - Treatment

Patient Received

1. 2 x LR 1,000 mL
2. No return to sports for 1 week
3. Consider metabolic myopathy

Final Diagnosis

1. Heat Exhaustion
2. Hyperuricemia
3. Elevated CPK
4. Acute kidney injury
5. Dehydration

Clinical Example #2a - Chief Complaint

21 yo African American M presented to the ED by EMS with shortness of breath following a wrestling tournament. Opponent placed the patient in chokehold causing the patient to pass out. When he regained consciousness, he had trouble breathing, difficulty swallowing, and a difficult time with his voice.

Thoughts?

Clinical Example #2a - Additional History

Patient has a history of a heart murmur and asthma. Also tells the ED that he has been "cutting weight" over the last several days, "hasn't been starving himself". Last urination was before today's match.

What's next?

Clinical Example #2a - Diagnostic Workup

CBC

BMP

CK

CK-MB

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Clinical Example #2a Laboratory Findings

Test	Patient #2a
General Chemistry	
CPK	**1220 (35-232 U/L)**
BUN	21 (8-25 mg/dL)
BUN/Creat Ratio	†
AST	†
Na+	137 (137-144 mmol/L)
K+	3.0 (3.6-4.8 mmol/L)
Macroscopic Urinalysis	
UA Color	†
UA Protein	†
UA Specific Gravity	†
UA Blood	†
Microscopic Urinalysis	
UA RBC	†
* = CK lab value † = no data available	

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Clinical Presentation #2a - Treatment

Patient received:

1. 2 x NS 1,000 mL
2. Dexamethasone 10 mg
3. Iopamidol 100 mL
4. Discharged and returned home with team

Final Diagnosis:

1. Choking injury
2. Mild rhabdomyolysis

Clinical Example #2b - C/C and History

Following day, patient woke up with dizziness and “felt bad” on and off all day. Patient presented to the ED by EMS following a syncopal episode in the dorm that evening.

Thoughts?

Clinical Example #2b - Diagnostic Workup

What would you order?

CBC
CMP
CK/CPK
UA

Clinical Example #2b Laboratory Findings

Test	Patient #2b
General Chemistry	
CPK	**>1,000 (55-170 IntUnit/L)**
BUN	18 (9-20 mg/dL)
BUN/Creat Ratio	14
AST	**65 (17-59 IntUnit/L)**
Na+	140 (136-145 mmol/L)
K+	3.3 (3.0-5.5 mmol/L)
Macroscopic Urinalysis	
UA Color	**amber**
UA Protein	30
UA Specific Gravity	1.02
UA Blood	**small**
Microscopic Urinalysis	
UA RBC	**6-10**
* = CK lab value † = no data available	

Clinical Example #2b - Treatment

Patient Received

1. 2 x NS 1,000 mL
2. Acetaminophen 650 mg
3. Zofran 4 mg
4. Meclizine 25 mg
5. Admitted overnight for observation and fluid resuscitation

Final Diagnosis

1. Recurrent Rhabdomyolysis
2. Mild hypokalemia
3. Inverted T waves - juvenile persistent pattern
4. Arachnoid cyst of the pineal gland

Clinical Example #3 - Chief Complaint

18 yo Caucasian M presents to the ED by ATC following a history of two syncopal episodes today. First syncopal episode earlier in the day, but second syncopal episode occurred in the locker room after wrestling practice and was witnessed. Patient was vomiting over the toilet when he passed out for approximately 1 minute. No other neurological deficits

Thoughts?

Clinical Example #3 - Additional History

Patient stated he had B/L flank pain that he rated as 3/10 along with other muscle cramping and aching. Patient has a history of colitis. Initially stated that he had been working out and was drinking water. Later admitted that he had not been drinking or eating because he was trying to lose weight for a wrestling match.

What's next?

Clinical Example #3 - Diagnostic Workup

CBC
CMP
CPK
UA

Clinical Example #3 Laboratory Findings

Test	Patient #3
General Chemistry	
CPK	**848 (55-170 IntUnit/L)**
BUN	19 (9-20 mg/dL)
BUN/Creat Ratio	16
AST	47 (17-59 IntUnit/L)
Na+	140 (136-145 mmol/L)
K+	3.9 (3.0-5.5 mmol/L)
Macroscopic Urinalysis	
UA Color	**amber**
UA Protein	3+
UA Specific Gravity	**>=1.030**
UA Blood	negative
Microscopic Urinalysis	
UA RBC	**‡**
* = CK lab value † = no data available	

Clinical Presentation #3 - Treatment

Patient received:

1. 2 x NS 1,000 mL
2. "CPK remains elevated but has trended downward. Patient should not be at any undue risk for discharge and continued oral water intake if he follows directions"

Final Diagnosis:

1. Elevated CK
2. Dehydration

Clinical Example #4 - Chief Complaint

18 yo Caucasian M presents to ED by ATC following a history of three syncopal episodes today after strenuous exercise. Stated he syncopal episodes occurred in the weight room earlier today. He felt very lightheaded and leaned up against the wall and felt as though he was going to pass out. Similar episode occurred on Monday (5 days earlier)

Thoughts?

Clinical Example #4 - Additional History

Once in the ED, patient denied any pain, but did note some muscle cramps in his hands and legs. Stated that he was trying to lose weight for an upcoming wrestling match and that he had not been eating or drinking much. Patient reports a history of migraines.

What's next?

Clinical Example #4 - Diagnostic Workup

CBC
CMP
CPK
UA

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Clinical Example #4 Laboratory Findings

Test	Patient #4
General Chemistry	
CPK	**>1,000 (55-170 IntUnit/L)**
BUN	**24 (9-20 mg/dL)**
BUN/Creat Ratio	20
AST	56 (17-59 IntUnit/L)
Na+	144 (136-145 mmol/L)
K+	4.0 (3.0-5.5 mmol/L)
Macroscopic Urinalysis	
UA Color	**amber**
UA Protein	30
UA Specific Gravity	**>=1.030**
UA Blood	negative
Microscopic Urinalysis	
UA RBC	**‡**
* = CK lab value † = no data available	

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Clinical Presentation #4 - Treatment

Patient received:

1. 2 x NS 1,000 mL
2. "No indication of any acute cardiac event. Normal kidney function. CPK trending downward"

Final Diagnosis:

1. Elevated CK
2. Dehydration

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CASE SERIES

Reevaluation of Diagnostic Criteria for Exertional Rhabdomyolysis in Collegiate Wrestlers: A Case Series and Review

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Abstract

Rhabdomyolysis is a common and potentially fatal condition encountered by athletic trainers, coaches, primary care physicians and sports medicine physicians. Benign, or physiological, Exertional Rhabdomyolysis (ER) may resemble Delayed Onset Muscle Soreness (DOMS) and becomes clinically significant when accompanied by other morphologies including severe muscle pain and swelling, and myoglobinuria. ER is often characterized by a triad of symptoms including 1) Muscle pain, 2) Muscle swelling, and 3) Myoglobinuria. Rhabdomyolysis and ER are associated with a variety of complications including metabolic acidosis, disseminated intravascular coagulation (DIC), hypocalcemia, hyperkalemia, arrythmias, compartment syndrome, acute renal failure, cardiac arrest, and even death. Risk factors including prolonged repetitive exercise that involves a heavy eccentric component particularly in extreme heat and humidity have been directly linked to the development of ER. Other major factors that have been linked to the development of ER include deconditioning, dehydration, electrolyte imbalances, nutrition and diet, drugs including diuretics, statins, Nonsteroidal Anti-inflammatory Drugs (NSAIDS), recreational drugs, dietary supplements, and high doses of caffeine. ER is often diagnosed as rhabdomyolysis in the emergency setting though this diagnosis may not be interchangeable in the presence of comparing the general population with the athletic population. CK/CPK is one of the most commonly used biomarkers in the diagnosis of rhabdomyolysis though CK/CPK levels ranging from 5 times to 50 times upper normal limits have been proposed in the literature. 5x upper limits of CK/CPK are often mentioned as being a conservative range for diagnosis, with no definitive pathological value for CK/CPK, healthcare providers should be aware that levels of 20x the upper limit may be seen in those performing repetitive and strenuous exercise(ee), with documented cases of CK/CPK laboratory values in excess of 130,000 IU/L to 244,000 IU/L in literature.

Keywords

Exertional rhabdomyolysis, Exercise induced rhabdomyolysis, Creatine Phosphokinase (CK/CPK)

Introduction

Rhabdomyolysis is a common and potentially fatal condition encountered by athletic trainers, coaches, primary care physicians and sports medicine physicians [1]. When the components of striated muscle such as the myofibrils and sarcolemma are damaged [1-6], cellular components including Creatine Kinase (CK/CPK) [1,2,4,5,7,8], Lactate Dehydrogenase (LDH) [1,7,8], Aspartate Transaminase (AST) [7,8], Alanine Transaminase (ALT) [7,8], calcium [3], potassium [1,3,4], myoglobin [8], and organic acids [3] are released in the surrounding plasma and extracellular space [5,6]. Exertional (exercise induced) Rhabdomyolysis (ER) is often diagnosed as rhabdomyolysis in the emergency setting though this diagnosis may not be interchangeable

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