Rhabdomyolysis & Heat Related Illness: Case Study

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Pathophysiology of Rhabdomyolysis

In its most basic terms, Rhabdomyolysis is a disorder of muscle catabolism resulting from the release of intra-cellular enzymes from injured myocytes into the bloodstream. The term literally means 'striated muscle breakdown or disintegration'.[1] The condition should be viewed as a potentially life threatening medical emergency. The disorder may be caused by any condition that results in damage to skeletal muscle, especially trauma. Myoglobin, an oxygen binding protein pigment is released into the bloodstream following skeletal muscle damage or trauma. The protein is filtered out of the bloodstream by the kidneys. Myoglobin may occlude the structures of the kidney, causing damage such as acute tubular necrosis or kidney failure. Necrotic skeletal muscle may cause massive fluid shifts from the bloodstream into the muscle, reducing the relative fluid volume of the body and leading to shock and reduced blood flow to the kidneys. The muscle injury associated with rhabdomyolysis is often described as irreversible cellular necrosis. However, if the insult is not too severe or prolonged, the myocytes maintain the potential to undergo repair without permanent muscle damage. This temporary release of intracellular products from myocytes into the plasma can still result in life-threatening illness and end-organ damage. [2]

Etiology of Rhabdomyolysis

- Disorder affects 1 in 10,000 people [1]
- Rhabdomyolysis was first described in the victims of crush injury during the 1940-1941 London, England, bombing raids of World War II. It has many etiologies.
- Incidence is higher in males than in females, especially in the subgroups of trauma and inherited enzyme deficiencies.
- 26,000 reported cases annually in the United States (AAFP) [1]

The process of rhabdomyolysis results from impaired production of adenosine triphosphate (ATP) by skeletal muscle or from the inability of the myocyte to meet increased metabolic demands from ATP. Specifically, the ATPase-dependent Na+-K+ pump is unable to maintain cellular homeostasis resulting in myocyte rupture due to increased intracellular water. When the cell membrane ruptures, intracellular enzymes are released into the bloodstream.[3]

Inadequate delivery of oxygen to the skeletal muscle results in anaerobic metabolism, which can compensate for hypoxemia in resting muscle for only a short period before cellular death occurs. Rhabdomyolysis develops when muscle ATP requirements exceed oxygen delivery and ATP production. This may follow drug withdrawal due to sympathetic discharge, participation in extensive strenuous athletic events, or prolonged involuntary muscle contraction as seen in neuromuscular disorders.[2]

Exercise-induced rhabdomyolysis has been reported as a result of military basic training, weight lifting, marathon races, ice skating, and other professional sports.[4] It appears that certain forms of exercise, such as downhill running, are much more damaging to skeletal muscle than other exercises such as weight lifting or uphill running. Another interesting fact is that athletes will have a larger reserve of stored myoglobin based on their cardiovascular endurance. Muscle cell hyperthermia due to strenuous exercise contributes to myocyte injury. Extreme exertion and hyperthermia inhibit ATP synthesis and result in disruption of the myocyte cell wall integrity with subsequent release of intracellular contents and eventual cell death. Hypoxia, glycogenolysis, and lactic acidosis are additional cofactors that contribute to skeletal muscle injury and subsequent rhabdomyolysis.[5]

Most patients with exertional rhabdomyolysis have confusion, pallor, and hyperthermia. The incidence of acute renal failure associated with all etiologies of rhabdomyolysis ranges from 30% to 40% but appears to be exceedingly low after exercise-induced rhabdomyolysis in the absence of nephrotoxic actors (hypovolemia, acidosis, aciduria, or renal ischemia).[4]

Risk factors include: [1]

Traumatic, Heat-Related, Ischemic and Exertional Causes of Rhabdomyolysis

Traumatic causes
- Lightning strike
- Immobilization
- Extensive third-degree burn
- Crush injury *(first discovery of Rhabdomyolysis came from crush injuries in WWII:1940)

Heat-related causes
- Heatstroke
- Malignant hyperthermia
- Neuroleptic malignant syndrome

Ischemic causes
- Ischemic limb injury

Exertional causes
- Marathon running
- Physical overexertion in untrained athletes
- Pathologic muscle exertion
- Heat dissipation impairment
- Physical overexertion in persons with sickle cell disease

Medications and Toxic Substances That Increase Risk of Rhabdomyolysis

Direct myotoxicity
- HMG-CoA reductase inhibitors, especially in combination with fibrate-derived lipid-lowering agents such as niacin (nicotinic acid; Nicolar)
- Cyclosporine (Sandimmune)
- Itraconazole (Sporanox)
- Erythromycin
- Colchicine
- Zidovudine (Retrovir)
- Corticosteroids

Indirect muscle damage
- Alcohol
- CNS depressants
- Cocaine
- Amphetamine
- Ecstasy (MDMA)
- LSD
- PCP
- Neuromuscular blocking agents

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LSD = lysergic acid diethylamide; MDMA = 3,4-methylene dioxymethamphetamine.

In August 2001, Bayer voluntarily recalled cerivastatin, marketed as **Baycol**, after 31 people died from rhabdomyolysis caused by the lipid lowering drug Baycol .

Clinical Presentation: Signs & Symptoms [1]

- abnormal urine color (dark, red, or cola colored) *usually initial tell-tale sign
- muscle tenderness and swelling
- paresis of the affected muscle(s)
- generalized weakness
- muscle stiffness or myalgia (aching)
- altered mental status
- anuria or oliguria (decreased urine output: < 500 ml in 24 hours).

Additional symptoms that may be associated with this disease:

- weight gain (unintentional)
- seizures
- joint pain
- fatigue

Tests & Measures

Physical examination reveals tender or damaged skeletal muscles. The diagnosis of rhabdomyolysis can be confirmed by means of certain laboratory variables. The most reliable indicator is creatine kinase (CK).

Creatine Kinase

- Assessing CK is most useful because of its ease of detection from serum and its presence in serum immediately after muscle injury.
- CK peaks in 24-36 hours and decreases at a rate of 36-40% per day. The serum half-life of CK is approximately 36 hours.
- Failure of CK to decrease suggests ongoing muscle injury. CK may also be elevated following myocardial damage or infarct.
- CK levels 5 times higher than normal suggests rhabdomyolysis and are frequently 100 times above normal or even higher.

Normal serum CK levels are 50 – 170 U/L. [18]

Myoglobin

- Measuring plasma myoglobin is **not** reliable because its half-life is 1-3 hours and it is cleared from plasma within 6 hours.
- The result may be false negative if myoglobin is not measured at the right time, however a positive urine myoglobin test result may help to confirm the diagnosis.
- Urine myoglobin is presumed if the urine is positive for blood but negative for red blood cells.
- A urine myoglobin assay is helpful in patients with coexisting hematuria (confirmed by microscopic examination) where myoglobin is suspected.

Complete blood count (CBC) including hemoglobin and hematocrit; serum chemistries including blood urea nitrogen, creatinine, glucose, calcium, phosphate, and uric acid; platelets; prothrombin time (PT); activated partial thromboplastin time (aPTT); serum aldolase, and lactate dehydrogenase are other useful laboratory tests that may be included.

- urinalysis may reveal casts and be positive for hemoglobin without evidence of red blood cells on microscopic examination.
- A urine or serum myoglobin test is positive.
- A CPK analysis is very high.
- A serum potassium may be very high (K^+ is released when cell breakdown occurs)

Medical Management & Treatment

Early and aggressive hydration may prevent complications by rapidly eliminating the myoglobin out of the kidneys. The hydration needs with muscle necrosis may approximate the massive fluid volume needs of a severely burned patient. This may involve intravenous administration of several liters of fluid until the condition stabilizes.

Diuretic medications such as mannitol or furosemide (Lasix) may aid in flushing the pigment out of the kidneys. If urine output is sufficient, bicarbonate may be given to maintain an alkaline urine state. This helps to prevent the dissociation of myoglobin into toxic compounds.

- Alkalinization of the urine and increased urine flow facilitates myoglobin excretion.

Hyperkalemia should be treated if present. Kidney failure should be treated as appropriate. Patients may undergo coagulation therapy (Coumadin, Lovenox) to prevent DVT, DIC or other coagulopathies.

Prognosis

The outcome varies depending on the extent of kidney damage incurred and exisiting co-morbidities as well as age of the patient.

Associated Complications

The complications associated with or resulting from rhabdomyolysis are numerous and range from mild to life threatening.

- **Early Complications**[1]
  - electrolyte imbalances: hypercalcemia, hypokalemia, *hyponatremia *(if exertional)
  - heart arrhythmias
  - cardiac arrest or myocardial infarct due to electrolyte imbalance
  - compartment syndrome: muscle swelling from excess extra cellular fluid can compress blood vessels and nerves *(early or late)
  - hepatic inflammation (~ 25% of patients)
  - hypovolemia – results from the massive ECF shifts resulting from myocyte necrosis. Up to 12 – 14 L of fluid may be sequestered by necrotic myocyte tissue contributing to hypovolemia.

- **Late Complications**[1]
  - acute tubular necrosis or renal failure (15% of patients)
  - disseminated intravascular coagulation (DIC) – this condition is typically worse 3 – 5 days following the onset of rhabdomyolysis.
  - *compartment syndrome– tight fascia (connective tissue) limits muscle expansion. Muscle expansion is already being stressed due to increased ECF shift. Peripheral pulses may still be palpable, but tell-tale sign will be complaints of sensory nerve deficits (numbness or tingling of the extremities or in a particular nerve distribution.) A delay of more than 6 hours in recognizing and diagnosing this complication can result in irreversible muscle damage or death! Decompressive fasciotomy should be considered if compartment pressures are > 30 mmHg.

- **Patient Background Information**

J.W.	19 year-old male
Diagnosis	Acute Exertional Rhabdomyolysis
Date of Onset	approximately 2 weeks prior
Admission Date	8/33/03
Discharge Date	9/2/03
LOS:	12 days
1° complaint:	muscle paresis & tingling dysesthesias at toes & bilateral ankles

- **History of Present Illness:** Patient was participating in his 2nd day of pre-season practice. He was returning to his dorm when he lost his ability to stand, had a visual distortion, described as 'fuzzy tunnel vision', resulting in a syncopal episode. Pt. was brought to Scranton CMC where hematologic testing showed elevated CPK values of 19,000. The patient was immediately consulted by Nephrologist, Dr. Yeager, who began aggressive hydration in order to preserve renal function. CPK levels on date of admission had decreased to 230.

- **Patient Social History**
  Patient is a sophomore criminal education major and starting outside linebacker at L. Junior College. Family resides in North Carolina. 8 siblings; 6 brothers and 2 sisters all who are healthy with no significant PMH. Father is an ordained minister with hx of diabetes mellitus. Mother is a licensed practical nurse with hx of HTN. Patient resides in on-campus dormitory housing.

- **Patient Medical History**
  Appendectomy, transient HTN and prior fracture of first 3 digits of ® hand. No prior surgical procedures or prior hospitalizations noted. Patients presenting symptoms were c/o musculoskeletal weakness, intermittent muscle pain and c/o sensory impairment in bilateral feet from the ankles to the toes.

- **Other Treatments**

  - Nursing:
    Medications
    1. Lovenox 40 mg Sub-Q q.d. (prevent coagulation; DIC)
       D/C'd once pt. was ambulating > 150'
    2. Senokot-S 1 tablet BID for constipation (possible 2° to dehydration)
    3. Vicodin prn for pain relief
    4. Ambien for sleep
    5. Tylenol
    6. Milk of Magnesia
    7. Dulcolax prn

  - Occupational Therapy: treatment primarily consisted of regaining bilateral upper extremity strength and dexterity. Additionally, patient's ADL status was assessed and continually evaluated.
  - Speech: no consultation warranted.
  - Psychology: no consultation ordered.
  - Dietary: no consultation ordered.
  - Recreation Therapy: no consultation ordered.

Summary of Physical Therapy Interventions

Prescription: evaluate and treat.

8/22/03: Initial contact. Review of HPI, PMH & status. Discussed treatment plan with patient.

8/23/03 Pt. presented with c/o fatigue, muscular weakness and soreness of bilateral UEs / LEs. Pt. required the use of a rolling walker due to excessive balance deficits and bilateral LE weakness and fatigue. Began basic gentle ROM of bilateral upper and lower extremities.

8/24/03 Pt. required W/C follow due to ambulatory tolerance of ~ 50' with RW. Moderate static and dynamic balance deficits present.

8/25/03 Began more aggressive extremity strengthening to tolerance. Rickshaw tricep extensions 30# bilaterally: 4 – 5 X 10, Cybex knee extensions: plate # 4 4 – 5 X 10 reps. Unilateral step-ups instructing patient to keep ankle in neutral position and touching bottom of heel to floor. Elevation training: 6" stairs Min A → CG using both HRs and step → step method.

8/26/03 Marked improvement of overall function noted. Quality of gait improved. Received orders for whirlpool/aquatic therapy. Performed 6" stairs using both HRs with CS using step over step method. Ambulatory tolerance was 300' with CG/CS no assistive device. CPK: 143. Lovenox D/C'd.

8/27/03 Initiated Aquatic Therapy. Began with gentle AROM exercises standing next to pool ladder. Marching in place, ankle pumps. Continued as follows: Heel to toe ambulation & lateral stepping with arms out at side to challenge but increase proprioception by using the force of buoyancy; ⇆ X 4. Performed hip flexion, abduction and extension standing instructing pt. to move LEs quickly enough to feel moderate resistance. Single limb stance activities using UEs prn to assist/maintain balance. Pt, was still fatiguing easily when endurance was pushed therefore progressions were based upon subjective reports, vital signs and observation of patient's overall status following exertional/endurance type activities.

8/28/03 2nd day of aquatic therapy worked on more progressive and functional tasks. Pt. worked on side stepping and shuffling drills with water up to neck level. Simulated running instructing pt. to break down running into components and move slower allowing water buoyancy to assist balance. Ended A.M. session with gentle LE cycling for a cool-down utilizing flotation device. Continued gait + elevation training, LE strengthening, and added manual stretching during P.M. session.

8/29/03 A.M. session was forgone in order for patient to participate in community outing to college. Touched based with patient's coach and made recommendations regarding patient's return to practice and full contact play. Recommendations included emphasis of slow return to prior functional status 2° to risk of relapse of condition or potential to sustain muscle or kidney damage if progressed too quickly. Additional recommendations were adequate hydration of patient and all players, as well as education on signs and symptoms of rhabdomyolysis. Provided patient's coach with journal articles on heat related illness and rhabdomyolysis. P.M. session initiated functional endurance/cardiovascular testing: warm-up of approximately 4 – 5 laps at normal walking pace around lower parking lot. Progressed to gentle jog around lot X 2 – 3 laps. 5' break. Attempted side shuffling drills to tolerance simulating task of 'scraping' the defensive line. At the end of the day issued general D/C instructions as well as a basic LE strengthening and UE/LE stretching program. Pt. was instructed to follow up with team ATC and physician. Only follow up services ordered was office visit to local physician to have hematologic testing to monitor liver & kidney function.

8/30/03 Patient given weekend pass to attend football game at college. CK ↑'d 219

9/2/03 Pt. D/C'd

Physical Therapy Goals:

STGs:

1. ↑ sit ↔ stand transfers to DS
2. ↑ dynamic standing balance to Fair + without RW.
3. ↑ ambulation to 300' with RW or HHA CS → DS and more normalized gait pattern.

LTGs:

1. educatce pt. on safety awareness with mobility/ambulation + importance of slow return to prior functional status
2. ↑ bilateral UE strength to 4 + → 5/5 or as able to allow pt. to return to prior functional status.
3. pt. will be independent with all transfer skills
4. ↑ standing static + dynamic balance → good
5. ↑ ambulation to 450' + independently without use of assistive device.
6. pt. will tolerate elevations as able.
7. increase cardiovascular endurance to 10 – 15 minutes of continuous aerobic activity.

FIM Scores

	Initial	D/C
AMB	1 / 7	7 / 7
ELEV	0 / 7	2 / 7*

***** progressing towards a 7

Conclusion:

Rhabdomyolysis is a potentially life threatening medical emergency if improperly managed. Physical Therapists must continually and thoroughly screen musculoskeletal complaints especially when risk factors for acute exertional rhabdomyolosis are present (poor physical endurance, inadequate hydration, excessive weight training, or exercising in extremely hot, humid weather etc,). With the passage of Direct Access laws for Pennsylvania, physical therapists must fine tune their differential diagnosis skills in order to determine if a patient's presenting musculoskeletal complaints and symptoms do or do not warrant immediate medical attention.

Heat Index Chart

The heat index chart combines the effects of heat and humidity to arrive at an apparent temperature. **Direct sunshine increases the heat index by 15°!**

Heatstroke occurs when the body's temperature exceeds 104°F

Relative humidity (%)

Air temperature (°F)	40	45	50	55	60	65	70	75	80	85	90	95	100
110	136												
108	130	137											
106	124	130	137										
104	119	124	131	137									
102	114	119	124	130	137								
100	109	114	118	124	129	136							
98	105	109	113	117	123	126	131						
96	101	104	108	112	116	121	126	132					
94	97	100	102	106	108	114	119	124	129	136			
92	94	96	99	101	105	108	112	116	121	126	131		
90	91	93	95	97	100	103	105	109	113	117	122	127	132
88	88	89	91	93	95	98	100	103	106	110	113	117	121
86	85	87	88	89	91	93	95	97	100	102	105	108	112
84	83	84	85	86	88	89	90	92	94	96	98	100	103
82	81	82	83	84	84	85	86	88	89	90	91	93	95
80	80	80	81	81	82	82	83	84	84	85	86	86	87

Heat Index/Heat Disorders

Heat index	*Possible heat disorders for people in higher risk groups*
Extreme danger 130°F or higher	Heatstroke/sunstroke highly likely with continued exposure.
Danger 105°F to 130°F	Sunstroke, heat cramps, or heat exhaustion likely, and heatstroke possible with prolonged exposure and/or physical activity.
Extreme caution 90°F to 105°F	Sunstroke, heat cramps, and heat exhaustion possible with prolonged exposure and/or physical activity.
Caution 80°F to 90°F	Fatigue possible with prolonged exposure and/or physical activity.

Reprinted from the U.S. National Weather Service. Retrieved March 2002 from: http://weather.noaa.gov/weather/hwave.html#HeatIndexChart.

Heat Cramps

Muscle cramps, which commonly occur in athletes and other physically fit persons, are caused by excessive heat exposure. Any activity that results in profuse sweating followed by too little or too much fluid intake can result in these painful muscle spasms, usually affecting the calf or abdominal wall muscles. Cramping is probably secondary to sodium depletion. [8]

During exercise, a poorly conditioned athlete may lose 1 to 2 L of fluid and 65 mEq per L of sodium per hour, whereas a highly conditioned, well-acclimatized athlete loses 3 to 4 L of fluid per hour with a sodium loss of only 5 mEq per L. Although more conditioned athletes lose less salt, they may take in excessive amounts of water, thus diluting their electrolyte concentrations and precipitating cramps. In addition, during more intense activity, a "slow" loss of sodium may occur over several hours to days, leading to cramps and progressing to other heat illnesses. [8]

Stretching the affected muscles and maintaining good hydration are important. Liberal intake of water is recommended, but this may induce hyponatremia if lost salt is not replaced. Commercial electrolyte solutions may help to prevent excessive salt loss, and a homemade formula of 1 tsp salt in 500 mL of water may also be used. Increased intake of dietary salt may be preventive. [8]

Signs and Symptoms of Potentially Life-Threatening Heat-Related Illnesses [8]

Heat cramps	**Heat exhaustion**	**Heatstroke**
Elevated body temperature	*Same as heat cramps,+ :*	*Same as heat exhaustion, +*:
Thirst	Nausea/vomiting	Anhydrosis
Muscle cramps	Headache	Delirium/seizure/coma
Sweating	Malaise/myalgias	Renal failure
Tachycardia	Hypotension	Hepatocellular necrosis
	Lightheadedness/syncope	Hyperventilation
	Oliguria	Pulmonary edema
	Uncoordination	Arrhythmia
	Confusion	**Rhabdomyolysis**
	Irritability	Shock
		DIC

Prevention and Treatment of Heat Stroke [8]

Prevention

- Prehydrate liberally with fluids
- Drink fluids before becoming thirsty
- Exercise in early morning/evening
- Treat pre-existing conditions
- Wear clothing appropriate for environment
- Check Heat Index Chart
- Acclimate over a 2-week period to get conditioned to exercising in the heat

Treatment

- Check airway, breathing, and circulation
- External cooling techniques
- Prehospital:
    1. Transfer to a cool, shady area
    2. Remove insulating clothing
    3. Apply ice packs to neck, axillae, and groin
    4. Douse with water
- In emergency department:
    1. Ice bath immersion
    2. Evaporative cooling
    3. Neuroleptics for seizures
    4. Mannitol/diuretics if needed to maintain urine output at 50 to 100 mL per hour
    5. Stop cooling at a rectal temp.ture of 100.4°F

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