

Endurance Training

SSE #42: Worst Case Scenarios: Exertional Rhabdomyolysis and Acute Renal Failure

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**SPORTS SCIENCE EXCHANGE
WORST CASE SCENARIOS: EXERTIONAL RHABDOMYOLYSIS
AND ACUTE RENAL FAILURE
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Key Points

- 1) Exertional rhabdomyolysis is the degeneration of skeletal muscle caused by excessive unaccustomed exercise. Symptoms of rhabdomyolysis include muscle pain, weakness, and swelling; myoglobinuria (presence of myoglobin in the urine); and increased levels of muscle enzymes and other muscle constituents in the blood.
- 2) Myoglobin in the urine causes the urine to darken in color. In rare cases, myoglobin can precipitate in the kidneys and cause renal failure. This has resulted in the death of some young, apparently healthy individuals.
- 3) Severe incidents of rhabdomyolysis tend to occur at the initiation of a training program when exercise is excessive and accompanied by heat stress and dehydration. Insufficient acclimatization, inadequate diet, and lack of specific physical conditioning may also contribute to this condition.
- 4) Certain individuals may be predisposed to rhabdomyolysis, possibly due to a latent metabolic disorder.

Introduction

On a warm September day in 1988, the members of the 12th class of 50 recruits began their first day of training at the Police Academy in Agawam, Massachusetts. Over the course of that day, the cadets performed numerous calisthenics, including sit-ups, push-ups, and jogging. Because of a problem with the water pipes in the old building housing the Academy, bottled water was brought in for the cadets to drink. (There was some question, however, as to whether the cadets had easy access to this water.) At 4:00 p.m. that day, a 25-year old cadet collapsed on the track during a run. He was rushed to a local hospital, diagnosed with acute renal failure, and put on dialysis. Forty-one days later, he died. Eleven other cadets were hospitalized, two of whom were placed on dialysis, and all survived.

On another September day in 1987, a 25-year old woman vacationing in the Grand Canyon collapsed after a four-hour walk down into the canyon. She became unconscious and was evacuated by helicopter to a local hospital. Hemodialysis was required for six weeks to compensate for renal failure. She subsequently recovered.

What these two examples have in common is the curious connection between strenuous exercise and renal failure. The common denominator in these situations appears to be a syndrome known as exertional rhabdomyolysis. Rhabdomyolysis is defined as a degeneration of muscle cells and is characterized by a group of conditions including muscle pain, tenderness, weakness, and swelling; myoglobinuria (presence of myoglobin in the urine); and increased levels of sarcoplasmic (muscle) proteins and other muscle constituents in the blood (Milne, 1988).

One of the proteins released from damaged muscle cells is myoglobin. High levels of myoglobin in the blood (myoglo-binemia) result in a "spill over" of myoglobin into the urine (myoglobinuria). In certain situations, myoglobin can precipitate in the kidneys and cause renal failure. The connection between rhabdomyolysis, myoglobinuria, and acute renal failure is complex and not completely understood. This review will describe the characteristics, incidence, causes, and consequences of rhabdomyolysis.

Myoglobin and Myoglobinuria

Myoglobin is an oxygen binding protein (mw 17,500) found almost exclusively in muscle tissue, although a small amount (6 to 85 ng/mL) is present in the blood. Myoglobin is not normally found in urine. When blood myoglobin concentrations rise to a range of 300 ng/ml 2 ug/ml, the renal threshold is reached and myoglobin "spills" into the urine (Penn, 1986). Myoglobin colors the urine, producing a range of light "iced-tea" to darker "Coca-Cola" colors.

Hemolysis (breakdown of red blood cells) will also result in a dark colored urine, as will bleeding of the bladder tissue. In these cases, the dark color is due to the presence of hemoglobin in the urine (hemoglobinuria) or intact red blood cells (hematuria). Exercise can cause intravascular hemolysis through impact, such as "foot strike" hemolysis in runners; exercise can also cause damage to the bladder that results in bleeding into the urine. It is important to distinguish whether dark urine is due to the presence of hemoglobin or myoglobin. This is because hemoglobin in the urine generally denotes a self-limiting condition, whereas the presence of myoglobin in the urine can produce damage to the kidneys.

There are several ways to differentiate the causes of dark urine. Hemoglobin is normally retained in the serum by binding to a specific protein, haptoglobin. When hemoglobin levels exceed the binding capacity of haptoglobin, the serum will become a red or brownish color, and hemoglobin will also be released into the urine. An increase in myoglobin in the blood (and consequently in the urine) does not cause a staining of the serum. This difference in clinical signs allows for a quick and simple differentiation of myoglobinuria from hemoglobinuria. Furthermore, with myoglobinuria, there typically are granular casts present that can be observed in a microscopic analysis of centrifuged urine samples (Milne, 1988). Other more precise laboratory analyses are also available to differentiate between myoglobinuria and hemoglobinuria (Hamilton et al., 1989; Penn, 1986; Schulze, 1982).

Rhabdomyolysis and Acute Renal Failure

Perhaps the first association between acute renal failure and darkly colored urine was

noted in London during World War II bombings that left patients suffering from crush injuries to muscles (Knochel, 1982). The mechanism by which myoglobinuria can lead to acute renal failure is not completely understood (Milne, 1988), but is thought to be due to renal tubular injury. While most cases of rhabdomyolysis result in myoglobinuria, only 5-7% of the cases of rhabdomyolysis result in acute renal failure (Barlett, 1985; Schulze, 1982).

In vitro studies have shown that myoglobin breaks down into ferrihemate and globin in an acid medium; ferrihemate damages the renal tubule epithelium, and transport of fluid and solute across the epithelium is then impaired (Knochel, 1982; Milne, 1988; Penn, 1986). The products of tissue breakdown form casts, which are thought to block the renal tubules (Penn, 1986). Renal blood flow is then restricted, leading to a fall in the glomerular filtration rate. The end result is renal failure. Animal studies have shown that myoglobin does not cause renal failure as long as urine flow is adequate (Knochel, 1982). Renal failure appears to be more likely when dehydration is present (Milne, 1986). The presence of heat stress is a common contributor in cases of acute renal failure.

Muscle samples taken from autopsy analyses of three cases of rhabdomyolysis with acute renal failure showed evidence of muscle fiber degeneration and a loss of myoglobin immunoreactivity (Nagashima et al., 1987). Furthermore, samples from the kidneys that were histologically stained for myoglobin showed fine granules in the epithelial cells of the distal tubules, and casts were found in the collecting ducts. Nagashima et al. (1987) concluded that myoglobin had leaked from the damaged muscle fibers and accumulated in the kidneys, thus causing renal failure.

Hyperkalemia, Hyperphosphatemia and Hypocalcemia

One of the most common electrolyte abnormalities associated with rhabdomyolysis is severe hypokalemia, an elevation of potassium in the blood (Honda & Kurokawa, 1983). Potassium is predominantly an intracellular cation and can be released into the circulation from damaged muscle cells (Honda & Kurokawa, 1983). Hyperkalemia can also result from renal failure, when the kidneys are unable to excrete potassium in sufficient quantity (Marieb, 1992; Milne, 1988). Hyperkalemia is found in about 50% of patients suffering from exertional rhabdomyolysis (Honda & Kurokawa, 1983). Excessive levels of potassium in the blood are potentially dangerous because they can interfere with the depolarization mechanisms in muscle by lowering the resting membrane potentials (Marieb, 1992). This may lead to abnormalities in heart rhythm and cardiac arrest and to weakness in skeletal muscle (Marieb, 1992).

Hyperphosphatemia (increased blood phosphate) is also associated with rhabdomyolysis (Knochel, 1982). The increased phosphate levels may be due to a release of phosphate from damaged muscle (Milne, 1988). Hypocalcemia occurs in the first 24 hours following exertional rhabdomyolysis (Honda & Kurokawa, 1983). This reduction of calcium in the blood is thought to result from the deposition of calcium in injured skeletal muscle cells (Honda & Kurokawa, 1983). Hypocalcemia can produce depressed excitability of heart muscle, and tremor and tetany in skeletal muscle (Marieb, 1992).

Blood Uric Acid, Creatine Kinase, Creatinine

Increased levels of uric acid in the blood (hyperuricemia) are common in cases of rhabdomyolysis (Knochel, 1982). The uric acid is probably produced by liver metabolism of adenine nucleotides, which are released from damaged muscle (Milne, 1988). Uric acid levels of 20-30 mg/dL (normal ranges are 3.3-7.5 mg/dL) often occur in conjunction with elevated blood concentrations of the muscle enzyme, creatine kinase (CK) (Knochel,

1982). Like myoglobin and uric acid, CK is also released from skeletal muscle (as are other muscle enzymes) when muscle damage occurs. In patients with major rhabdomyolysis, the serum CK activity may increase to 100,000 U/L or more (normal range is 22-198 U/L) (Knochel, 1982). In the case of the 25-year old woman mentioned in the introduction, her CK level upon entry into the hospital was 1,600,000 U/L (Pattison et al., 1988).

Rhabdomyolysis also causes a fast-rising serum creatinine concentration, as creatine released from damaged muscle is rapidly dehydrated to creatinine. In evaluating acute renal failure of unclear cause, finding that the serum creatinine concentration is higher than expected for the concentration of blood urea nitrogen is a strong clue that rhabdomyolysis is the culprit.

Rhabdomyolysis In the Military

In the late 1960s, eight young men who were in a training program for naval aviation officer candidates were referred to the Naval Aerospace Medical Institute for evaluation of grossly discolored urine and severe muscle pain (Smith, 1968). Each of the men had participated in novel strenuous exercise within 38 hours prior to detection of the myoglobinuria. The exercises included 42-100 pushups or 20-25 pushups along with leg lifts or straddle hops. These calisthenics were often assigned by the drill instructors for minor violations of cadet rules. All eight recruits reported impaired muscle function and demonstrated elevated blood levels of muscle enzymes. Restoration of functional capacity took several weeks.

Demos and Gitin (1974) reported that 40 Marine Corp recruits were hospitalized at the Naval Hospital in Beaufort, South Carolina, following several days of excessive upper body calisthenics. Many reported dark urine, and all were diagnosed with exertional rhabdomyolysis. Additionally, at the U.S. Army Hospital in Fort Jackson, South Carolina, six cases of myoglobinuria and muscle pain were reported in 1959 in recruits undergoing Army basic training (Turell, 1961).

Thirty-three (5.5%) of 586 recruits in the first two weeks of training at an Officers Candidate School in Fort Benning, Georgia, demonstrated brown urine and other symptoms of rhabdomyolysis (Greenberg & Ameson, 1967). Two to three weeks were necessary for recovery of muscle function for most individuals. However, after six weeks, eight recruits still displayed muscle weakness, and after three months, one subject was still weak. Muscle biopsy samples obtained from three of the military recruits demonstrated small muscle fibers with abnormal histological staining patterns. Interstitial inflammation was prominent, with large numbers of lymphocytes, macrophages, and neutrophils. The clinical diagnosis was "myopathic lesion manifested by widespread regeneration and inflammation" (Greenberg & Ameson, 1967).

In each of these reports, strenuous, repetitive, calisthenic-type exercises (push-ups, pull-ups, squats) performed on the first few days of training produced rhabdomyolysis, but not renal failure. The excessive repetitions of the same exercise would classify them as novel to most individuals. Because of the principle of exercise specificity, few of these recruits would have been conditioned for this type of exercise (Demos et al, 1974).

Rhabdomyolysis in Athletic Performance

Schiff et al. (1978) studied 44 runners who completed a 99 km road race and found that 25 of them demonstrated increases in blood levels of myoglobin, CK, and other muscle enzymes. Myoglobin was detected in the post-race urine samples of only six runners.

Acute renal failure was not observed in any of these subjects. In another study, 24 athletes who had competed in a triathlon showed a dramatic rise in serum myoglobin and reported muscle pain, but none required hospitalization (Schiff et al., 1978).

A report in 1988 stated that three young men who, after participating in the first session of a body building exercise program, complained of muscle pain and dark urine (Doriguzzi et al, 1988). All had regularly engaged in sport activity (but not body building exercises) prior to the exercise session. The rhabdomyolysis incurred was self-resolving for these men. In another study, Zajaczkowski et al. (1991) reported a case of an individual who developed rhabdomyolysis and heavy myoglobinuria after vigorously playing squash. He was treated with diuresis therapy and did not develop renal failure.

In contrast, not all dark urine in athletes is due to rhabdomyolysis. Sometimes hematuria (intact red cells) causes the dark color of urine, as in the following two reports. Fred and Natelson (1977) reported cases of 13 men with "grossly bloody urine" that appeared sporadically during endurance running training. The dark urine appeared benign, resolving on its own. Siegel et al. (1979) examined urine samples from 50 marathon runners before, immediately after, and on three successive days following a marathon race. Hemoglobin was found in the urine of nine subjects. This condition was self-limiting and considered to be the result of mild damage to the bladder that caused bleeding into the urine (Fred & Natelson, 1977; Siegel et al., 1979). "Bloody urine" in marathon runners is common and is generally not due to rhabdomyolysis (Fred & Natelson, 1977).

Rhabdomyolysis and Acute Renal Failure

There appears to be an association between heat stroke, rhabdomyolysis, and acute renal failure. Thomas and Motley (1984) noted that serum myoglobin levels were significantly correlated with post-exercise body temperatures in 24 subjects who completed a triathlon. In none of the reports on military recruits and athletes cited in the two sections above was any individual diagnosed with acute renal failure. Most of these studies did not report body temperatures of the subjects upon admission to the hospital, so temperatures were presumably normal. In the two studies where body temperatures were reported, they were normal (Smith, 1968; Turell, 1961).

Vertel and Knochel (1967) documented renal failure in 10 army recruits who had participated in their first sessions of basic training during the period from 1958-1965. Two of the recruits died. An autopsy of one individual revealed extensive necrosis of pectoralis muscles. A fasciotomy of the anterior tibialis muscle was performed on another individual; it revealed extensive necrosis of the anterior tibialis muscles. All 10 recruits had experienced heat stroke or heat stress, and their state of hydration was compromised.

The effects of rhabdomyolysis on the kidney appear more pronounced when one is dehydrated (Knochel, 1982). The fatally afflicted police training cadet mentioned in the introduction had exercised at an ambient temperature (80-83° F) that was not high enough to cause heat stroke, but sufficiently high to result in body water loss through sweating (Hassanein et al, 1991). Moreover, access to fluids was restricted for these cadets. The cadet's temperature upon admission to the hospital was 105° F (rectal), and he presented classical signs of heat stroke (Hassanein et al., 1991).

However, one recent study provides evidence that dehydration and heat stress are not absolute prerequisites for exercise-induced renal failure. Uberoi et al. (1991) reported that within a six year time period, seven healthy, active individuals developed renal failure after performing a cross-country run of 10-15 km (n=6) or after a three day march of 90 km (n= 1). No evidence of heat stress, dehydration, or hypotension was found in any of these

individuals. Indications of rhabdomyolysis, including myoglobinuria (n=7), hypocalcemia (n=3), and hyperkalemia (n=4), were present, and subjects required dialysis. The mean blood CK level for these subjects was 120,000 U/L.

Inter-individual Variation

Although the data on exertional rhabdomyolysis are alarming, it should be noted that only a relatively few severe cases have been recorded. In the study of four classes of Officers Candidate School students, only 23 cases of proved myoglobinuria associated with physical activity were found among 586 individuals (Greenberg & Ameson, 1967). However, through the course of the study, the extent of physical training may have changed for the 3rd and 4th classes because of the reported incidence of rhabdomyolysis in the previous two classes. In the example cited in the introduction, of the 50 police training cadets, 11 were hospitalized and three required dialysis. Of the 16,506 candidates who took a firefighter fitness test in New York during 1988-1989, 32 were hospitalized with renal failure (Morbidity and Mortality Weekly Report, 1990). The young woman described in the introduction who walked down the Grand Canyon was accompanied by other members of her group, and her fluid intake was similar to that of the other members. Her fellow hikers were apparently symptom free; this was fortunate because they carried her to safety (Pattison et al, 1988).

Why are some individuals more susceptible to rhabdomyolysis? From the literature it is well documented that a novel strenuous exercise will produce muscle damage (Clarkson, 1990). Therefore, the specificity of exercise training is important. Even if an individual is trained in one activity (e.g., endurance running), this training may provide little or no "protection" if 100 push-ups or repetitive squat-jumps are performed.

Some individuals may have an hereditary sub-clinical muscle enzyme anomaly or other defect (Noakes, 1987). Under normal exercise stress their condition would probably go unnoticed. However, performance of very strenuous, repetitive, unaccustomed exercise may exacerbate muscle damage such that the defect becomes apparent. Also, in a competitive event the zeal to win or the shame of quitting may provide the coup de grace that will allow some individuals to go beyond a tolerable level of muscle injury (Knochel, 1990).

The physical condition of an individual when performing strenuous unaccustomed exercise may be a factor in determining susceptibility to rhabdomyolysis. A subject in our laboratory who produced dark urine after performing maximal eccentric actions of the forearm flexors developed respiratory flu-like symptoms on or about the day of exercise. Also, his job required him to work nights, and he was staying awake longer during the day to study for upcoming final exams. To keep awake he drank a considerable quantity of coffee, which may have produced a mild state of dehydration. These factors were considered potentially influential because about one month prior to this bout of damaging exercise he had performed the same exercise with the opposite arm, and no adverse effects occurred.

Anecdotal information from a few runners has been used to implicate diet in susceptibility to rhabdomyolysis (Bank, 1977; Knochel, 1990). Knochel (1990) cites the case of a 34-year old avid runner who performed an exercise and diet manipulation to increase muscle glycogen stores prior to a 10,000 meter race. The manipulation involved performance for a 10,000 meter run three days before the race to lower the muscles' glycogen stores. This was followed by consumption of a high carbohydrate diet on the day before the race to "glycogen load." He completed the race, which took place at an ambient temperature of 87° , and then collapsed. Within 30 minutes he was admitted to a hospital, where his CK value was 37,000 U/L. He died shortly thereafter due to rhabdomyolysis and heat stroke.

Bank (1977) cites two other cases of well-trained runners who performed the carbohydrate loading technique and had brown urine after running. One required treatment for renal failure. It should be emphasized that the practice of glycogen loading has been performed by numerous athletes with no negative effects. Bank (1977) suggested that the glycogen loading practice may predispose certain susceptible runners to the hazards of myoglobinuria.

Why the diet should have an effect on muscle damage is unclear. Knochel (1990) suggested that the increased glycogen could result in greater production of lactate and, hence greater muscle acidosis. Furthermore, Knochel noted that exertional rhabdomyolysis appears more likely in fasting athletes who perform strenuous work (Knochel, 1982). Perhaps a disruption in normal muscle energy stores, whether increased or decreased, may impair muscle function in susceptible individuals who exercise strenuously.

A common feature in prior cases of renal failure accompanying rhabdomyolysis was that the ambient temperatures were generally high such that many of the individuals appeared to suffer from heat stress, i.e., either profuse sweating or heat stroke. Some individuals may be more susceptible to heat stress than are others. Heat stress susceptibility is certainly influenced by the state of hydration of the individual as well as by the state of acclimatization.

Legros et al. (1992) identified six subjects who suffered from exertional heat stroke and rhabdomyolysis. These subjects, along with eight sedentary men with no past history of heat stress, performed hand dynamometer exercise using repeated contractions. On the last set of contractions, a cuff was placed on the arm and inflated to reduce arterial flow. During the exercise, the forearm flexor digitorum superficialis muscle was examined using ³¹P-NMR spectroscopy. No differences were found between the two groups of men at rest. In both groups, the concentrations of creatine phosphate and the muscle pH were reduced after exercise. However, the changes were greater for the subjects who had suffered previous heat stress. These differences between groups became more dramatic when blood flow was restricted, and recovery was slower for the subjects who had experienced prior heat stress. Legros et al., (1992) suggested that the large decrease in muscle pH for these subjects may cause an abnormal cellular acidosis, which has been implicated in rhabdomyolysis (Knochel, 1990). The individuals who had suffered prior heat stress may have a persistent, latent metabolic disorder that predisposed them to heat stress and rhabdomyolysis.

Brown and Mitchell (1991) reported a case of heat stroke and rhabdomyolysis induced by strenuous exercise without sufficient fluid intake during three days of military training. An apparently healthy 24-year old man collapsed while running. Despite efforts to stabilize him, his CK levels remained elevated for five days and again increased dramatically four days later. The results of ³¹P-NMR spectroscopy performed after the patient had recovered were similar to those of the study by Legros et al. (1992) cited above. There was a delay in recovery of muscular pH after exertion in this individual.

An Ounce of Prevention and a Pound of Cure

Most cases of heat stress, rhabdomyolysis, and acute renal failure have occurred during the first days of military training, during which excessive repetitive exercises (e.g., push-ups, squat jumps) have been used. The military is now aware of this potential hazard, and the use of these forms of exercise as punishment has been restricted. Many police training policies have also limited these dangerous practices. (This author served on the Governor's Panel to Review Police Training Programs in Massachusetts that was

established after the incident described in the introduction.)

Certainly, coaches or fitness counselors should never begin a training season using repetitive, or strenuous, unaccustomed exercises. In a case study of one sedentary, mildly overweight, 28-year old man, a fitness counselor instructed him on the first day of training to perform a series of intense exercises (Coward, 1990). For 10 minutes he peddled as hard as possible on a bicycle, rowed for 10 minutes on a rowing machine at peak effort, and walked at a fast pace on a treadmill for 10 minutes. The next day the man phoned the fitness counselor to describe the severe muscle pain and stiffness that he was experiencing. The fitness counselor recommended that he return. After a light massage, the counselor advised the man to repeat the regimen he had performed the day before. The man was admitted to the hospital the following day because of dark urine and was diagnosed with rhabdomyolysis. On the second day, renal failure developed and he was placed on dialysis for 11 days.

In a previous Sports Science Exchange article, it was suggested that all exercise training should begin with mild intensity exercise and should gradually build up to an appropriate level (Clarkson, 1990). The reason for this recommendation is to prevent undue muscle soreness on subsequent days. Additionally, for those individuals predisposed to severe exertional rhabdomyolysis, starting up gradually could save their lives.

Other factors that should be considered before performing strenuous exercise in a warm/hot environment are degree of acclimatization, diet, and fluid intake. Athletes should be advised not to try any new diet manipulation for the first time prior to a strenuous competitive event, nor should they use diuretics. Most diuretics lower blood levels of potassium and promote dehydration, thereby exacerbating muscle damage. Because dehydration is implicated in rhabdomyolysis, adequate fluid should be available and ingested before and during exercise. These ounces of prevention are worth many pounds of cure.

Some individuals who have never had any prior related symptoms have run a marathon or performed other strenuous recreational activities and collapsed, requiring hospitalization. These rare cases are tragic and disturbing. When an athlete collapses from overexertion and/or heat stroke, the "pound of cure," i.e., prompt treatment, is imperative. Most individuals who receive immediate medical attention survive. However, the recovery may be very slow. In the case of the woman who had hiked down the Grand Canyon, hospitalization was necessary for seven weeks. In the case of one of the military trainees in Officers Candidate School, hospitalization was required for three months, and muscle weakness was still apparent five months after the episode of exertional rhabdomyolysis.

Summary

Exertional rhabdomyolysis is characterized by a syndrome of conditions including muscle pain, weakness, and swelling; myoglobinuria; and increased levels of sarcoplasmic proteins and other muscle cellular constituents in the blood. Generally, this syndrome is brought on by the performance of unaccustomed, excessive, repetitive exercises such as push-ups and squat-jumps. Rhabdomyolysis can also occur after strenuous recreational activities such as marathon running, hiking, or performance of excessive strenuous exercise during the first days of a new training program. Mild cases of rhabdomyolysis do not require hospitalization, and individuals recover within one week. However, in certain individuals, rhabdomyolysis can be severe. The combination of heat stress (hyperthermia) and rhabdomyolysis can produce acute renal failure, which, in rare instances, can result in death. The few individuals who have developed severe rhabdomyolysis generally have never shown any prior symptoms. These individuals may have a latent, sub-clinical

muscle disorder that predisposes them to the most negative consequences of rhabdomyolysis. For strenuous exercise in the heat, precautions such as adequate fluid intake and acclimatization are critical. All exercise training programs should start with mild to moderately intense exercise and should progress gradually. These safeguards will not only prevent subsequent muscle pain and optimize performance, but they may also save lives.

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