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Muscle dysfunction during physical activity – muscle rhabdomyolysis

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Abstract
Rhabdomyolysis is the breakdown of striated muscle fibers, which results in the release of muscle cell components into the peripheral circulation. Most cases of rhabdomyolysis are the result of trauma, often a consequence of seizures, alcohol and drug abuse but in some cases it is associated with very intensive physical activity. Proper understanding of muscle rhabdomyolysis can contribute to better preparation of sportsman for the intensive physical activity and to protect his body from episodes of extensive muscle breakdown and prevent their occurrence.

This article is a attempted to summarize and show medical and biochemical basics of muscle rhabdomyolysis with a special attention to the episodes that occurs during physical activity. It may help in prevention of such cases in the future and protects the body of a sportsmen.

Keywords: rhabdomyolysis, physical activity, myoglobin, muscle

Introduction

Building the right level of muscle mass is one of the key factors determining the achievement of high sports results, but it is also one of the important factors of the attractiveness of the human body (Phillips and Hill, 1998; Andreoli et. All 2001). Moreover, the proper development of muscle tissue is recognized as a key factor necessary to maintain adequate health ((Hikida, 1983; Heithoff et. All 1997).

Rhabdomyolysis is the process of breaking down muscle strings, which results in the transfer of muscle cell components to the peripheral circulation [Vanholder, 2000; Warren et. All. 2002]. One of the most important compounds released into circulation is myoglobin, a protein contained in striated muscles, which contributes to the storage of oxygen. Structurally, the myoglobin molecule, analogically to hemoglobin, is classified as a protein. The myoglobin released into the circulation is filtered and excreted into the

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urine, which can damage the kidneys. The renal threshold is 15 mg / 100 ml of myoglobin in the blood serum. The presence of myoglobin in the urine indicates significant muscle damage. It is assumed that about 200 g of muscle breakdown can lead to myoglobinuria. Lumps and rollers clog the renal tubules, causing the vessels in the ball and capillaries to contract, leading to drainage disorders. They lead to the death of the distal tubules and kidney failure. During the breakdown of muscle fibers, creatine kinase often increases, which is a marker of renal filtration disorders. Rhabdomyolysis is reported to be one of the leading causes of acute kidney injury (ARF). However, it should be remembered that not every case of ARF is associated with rhabdomyolysis, and not every case of muscle breakdown results in acute nephritis. In most cases, rhabdomyolysis is the result of trauma, often a consequence of seizures, alcohol abuse, and drug abuse [Vanholder, 2020].

To diagnose the ER disease entity, urine tests for myoglobin and blood tests are necessary, where the activity of muscle enzymes (rheratin kinase, lactate dehydrase), potassium and calcium levels are measured [Vanholder, 2020].

Etiology

One of the causes is injuries due to high-voltage electric shock (e.g. lightning), resulting in myolysis due to disruption of the sarcolemic membranes, resulting in pore formation, loss of barrier function, and increased calcium permeation through the membrane [Eiser, 1982].

Raised body temperature (e.g. from infection) can also cause rhabdomyolysis. In connection with hyperthermia, neuroleptic malignant syndrome develops, which is characterized by high fever in patients treated with phenothiazides or haloperidol [Eiser, 1982]. Another potential cause is malignant hyperthermia, an inherited condition characterized by a rapid increase in body temperature (1°C/5min), usually after anesthesia [Abraham, 1997]. As a result of excessive sweating, these patients also often have hypokalemia, which can worsen muscle damage. The breakdown of muscle fibers is noticeable in some hereditary diseases. These disorders usually occur in childhood, and careful observation is required whether myolysis occurs in the manner that usually occurs in healthy people or occurs without the interference of external factors. If ER recurs in a healthy young patient, hereditary muscle enzyme defects should be considered.

The most common are carnitine palmitoyl transferase deficiency, myophosphorylase deficiency (McArdle's disease) and adenosine monophosphate deaminase deficiency. Electrolyte disturbances are closely related to the breakdown of muscle fibers. Hypocalcaemia, i.e. insufficient level of calcium in the blood (below 2.25mmol / l). Hypophasphataemia (phosphorus deficiency in the blood serum - below 0.9 mmol / l) contributes to a decrease in ATP synthesis. Hyponatraemia and hypernatmia, disorders of sodium metabolism in the body and hyperosmotic states. The causes of these conditions can be excessive alcohol consumption, as well as severe malnutrition, disease or malabsorption of the elements. Changes in cellular metabolism - stretching of sarcoplasmic membranes increases and an influx of sodium, chloride and water occurs, which causes cell swelling and self-destruction [Poels, 1993]. Calcium enters the cell in exchange for intracellular sodium. Large amounts of free calcium ions induce persistent contraction, leading to energy depletion and cell death [Brumback, 1992]. In addition, calcium activates phospholipase A2 as well as various vasoactive molecules and proteases. In addition, it leads to the production of oxygen free radicals. The damaged muscle is attacked by activated neutrophils, which amplify the damage by releasing proteases and

free radicals. Consequently, inflammation occurs, a self-sustaining molar reaction instead of pure necrosis. Very intense muscle exercise can cause myolysis in untrained people or in those who exercise in extremely unfavorable conditions, e.g. in very high temperature and high humidity. Muscle necrosis is much more common when going downhill than in ascents or climbs. The combination of muscle exertion, hypoxemia, and corticosteroid-induced myopathy can cause myolysis, exercise causes faster muscle ischemia in hypokalemia [Knochel, 1990].

Exercise rhabdomyolysis

Exercise rhabdomyolysis is a common phenomenon, most likely occurring in a mild form by anyone who has performed exercise, as it is perceived as muscle stiffness. Within 24 hours after heavy physical stress, a set of characteristic ailments develops. They especially affect the legs, especially the calves. Increasing pain leads to muscle tension, swelling and contracture. The patient is lying in bed, unable to move. Myoglobinuria lasts until disease peak, most commonly 4 to 6 days. The pain gradually subsides after about 1-2 weeks. Sometimes slight paresis remains. The disease most often affects young men [Knochel, 1990].

If serum CK was measured at this time, a slight increase in serum CK would be noticeable. Some of the most classic examples of rhabdomyolysis occur among the best trained endurance runners. In the subjects, subsequent muscle tests showed no results suggesting a hereditary myopathy, but carnitine palmityl transferase deficiency or other myopathy. For this reason, it is assumed that any normal person can develop rhabdomyolysis, provided that the triggers for it are sufficient. Strenuous exercise, especially during the competition, and especially when the athlete makes every effort to win in the final stage of the competition, provocative factors. Hot or warm weather and high humidity increase the risk considerably. Victims of this disorder report that they continued to exercise despite cramps, pain, and a feeling of numbness in their lower limbs. Some of them kept running despite feeling confused. Observers of these struggles usually reported that the players had pale skin, as if their blood vessels had narrowed, which could be explained by massive norepinephrine discharge or, alternatively, their cardiac output and peripheral circulation had failed. It appears that during the final stage of the competition, the patient develops severe soft tissue damage, and in some cases heat stroke is a concomitant disease. The state of acute exercise rhabdomyolysis is often underestimated by doctors who deal with players right after the competition. While most patients recover quickly, some develop potentially fatal metabolic acidosis or hyperkalemia, which may develop over the next 24 hours [Hikida, 1983].

Symptoms of the disease are often underestimated in the early stages, while its accurate diagnosis and treatment of complications can save lives. There is evidence that training causes some degree of resistance to the development of exercise rhabdomyolysis as exercise heat stroke, however, a well-trained athlete can still develop exercise rhabdomyolysis. Physical training is a kind of adaptation, it helps to protect the body against the effects of exercise, it helps to reduce heat excretion, thanks to which there are fewer physical complications. Training helps to reduce the incidence of exercise rhabdomyolysis, but does not completely protect against it. One of the most important adaptation elements is the adaptation of the cardiovascular system to exercise. According to Brodthagen (1983), cardiac output increases significantly after training and resting heart rate is lower. These changes are noticeable after a week of regular training. They are

characterized by an overall increase in blood volume, an increase in the volume of plasma and albumin circulating in it [Convertino, 1980]. There is also an increase in capillaries surrounding the muscle fibers, which in turn increases blood flow through the muscle cell [Brodal, 1977]. The increased blood volume and increased red blood cell mass help maintain oxygen delivery to the working tissue. During training, the amount of myoglobin in skeletal muscles increases, which allows the delivery of more oxygen to the mitochondrion, which in turn has an impact on maintaining the production of ATP [Adiseshiah, 1992].

In the research conducted by Del Coso (2013), participants of the marathon run were examined, blood analysis was performed before and after the run, urine analysis and biopsy of the gastrocnemius muscle. The aim of the study was to determine what factors influence the maintenance of a constant speed of runners during the marathon. As the authors stated, completing a marathon can severely damage the muscle fibers [Hikida, 1983] and cause the release of muscle protein (mainly myoglobin) into the bloodstream [Schiff, 1978]. By performing a biopsy of the gastrocnemius muscle before and after the marathon, it has been proven that running a marathon distance causes necrosis and inflammation of the muscle fibers [Hikida, 1983]. These muscle abnormalities correlated with clinical reports of rhabdomyolysis [Hikida, 1983], additionally, there was a correlation between the presence of myoglobin in the urine and a decline in performance during the marathon.

Tab. 1 Blood serum results before and after the marathon race in rhabdomyolysis (according to Del Coso 2013)

Variable	Pre	Post
Osmolality (mOsm/kg H^2O)	289 ± 4	297 ± 6
Glucose (mmol/L)	5.2 ± 0.8	5.8 ± 1.2
Myoglobin (µg/L)	45 ± 12	952 ± 1064
CK (U/L)	176 ± 98	453 ± 348
AST (U/L)	30 ± 8	45 ± 15
ALT (U/L)	27 ± 13	26 ± 11
GGT (U/L)	39 ± 37	37 ± 35
Urea (mmol/L)	5.8 ± 1.2	7.3 ± 1.3
LDH (U/L)	379 ± 68	630 ± 142

Internal muscle dysfunction is often seen when the muscle is overloaded (muscle fibers break down during work), causing rhabdomyolysis associated with vigorous long-distance runners. If not treated quickly, complications such as acute kidney failure can occur. In 2001, the case of [Wong, Yeung] of a 30-year-old woman who presented to the hospital with hematuria after running a marathon was reported. The general condition of the patient was good, she did not complain of any muscular pains or lower abdominal pain. Blood tests were performed, in which an increase in CK - 1070 IU/L was found. There were also tests for rhabdomyolysis. The test for myoglobin in the urine confirmed the patient's rhabdomyolysis. During rhabdomyolysis, there was an enzymatic destruction and dysfunction of mitochonders in muscle cells, which leads to changes in the blood,

including myoglobin, creatine kinase, potassium, uric acid, phosphates and others. Due to the release of these components into the blood, the filtration function of the kidneys was disturbed, which resulted in haematuria. Interestingly, rhabdomyolysis in women is much less common than in men [Wong, Yeung, 2001].

Rhabdomyolysis in women

Rhabdomyolysis associated with septic shock, electrolyte disturbances, mineral deficiencies, drug and alcohol abuse appear to occur with equal frequency in both men and women. However, exercise rhabdomyolysis and exercise heat stroke are virtually unheard of in women. This is interesting because an increasing number of women participate in competitive endurance races [Knochel, 2003].

Differences in response to exercise-induced muscle damage between males and females have been noted and discussed in relation to the protective role of the female sex hormone estrogen [Kendal, 2002]. Through the high antioxidant capacity of estrogen, the stabilization of membrane properties, or the regulatory effect of genes or the complex interplay of these properties. The lower creatine kinase responses shown by women after exercise-induced muscle damage [Krieder, 2003] do not conclusively suggest that estrogen alleviates the muscle damage process because functional measures usually suggest that the hormone is ineffective in minimizing muscle damage [Rogers, 1985]. Therefore, more research is needed to quantify the role of estrogen in muscle damage.

In the studies of Shumate et al. (1979) investigated the effect of 120 minutes of exercise on a bicycle ergometer, the effort was moderate. the subjects had blood drawn before, during, immediately after and 72 hours after training. Venous blood lactate levels remained unchanged. Baseline CPK values were higher in men, most likely the cause was greater muscle mass in men. Twenty-four hours after training, men had a mean CPK of 664 IU / liter compared to 152 IU / liter for women. The authors suggested that the symptoms of muscular dystrophy in men may be related to the X chromosome. They also indicate that diethylstilbestrol (an oral drug, non-steroidal estrogen) reduces CK, suggesting that estrogens may be a protective factor for CPK. In fact, when exercises are performed that are predominantly eccentric (for example, going downhill) as opposed to predominantly concentric contractions (such as climbing stairs with muscles tense), the gender difference is not significant [Nicholson, 1986].

The explanation for the lack of exercise rhabdomyolysis in women is not obvious. Some studies of body temperature when working in hot environments indicate that women are able to cool off more effectively than men due to the amount of work done by the body, body surface area or by having more body weight [Bransword & Howley, 1977]. This shows that men secrete a greater amount of sweat under conditions of elevated temperature as well as a result of evaporation under comparable working conditions [Wong, Yeung 2001].

Metabolic disorders during rhabdomyolysis

The release of the necrotic muscle components causes changes in the plasma concentration of inorganic and organic compounds that can lead to life-threatening complications. The accumulation of these compounds worsens the condition of the already disturbed glomerular filtration of the kidneys. There is necrosis with accompanying inflammation, there is an exudation of fluid outside the cell and swelling of the limb - fluid accumulates in them. The release of organic acids from dying muscle cells causes acidosis with a high anion gap. Hypoxic muscles release lactic acid (which results from the use of glucose during anaerobic combustion) into the circulation; its removal by the liver is insufficient if the patient is hypovolaemic. Acidosis impairs metabolic functions and may increase hyperkalemia. Lower urine pH and intraocular acidosis will facilitate the interstitial precipitation of myoglobin and uric acid. In the early stages of rhabdomyolysis, calcium builds up in the muscles. In the presence of hyperkalaemia, severe hypocalcaemia may lead to cardiac arrhythmias, muscle spasms, or convulsions, which may further damage the muscles. In the later stages of the disease, the accumulated calcium is released from storage. It is often associated with hyperparathyroidism and hypervitaminosis D and overt hypercalcemia. However, hyperparathyroidism and D hypervitaminosis are not evident in all cases. Hypercalcaemia is more common in the presence of calcium supplemented during the hypocalcaemia phase. Phosphorus is released from damaged muscle and accumulates in patients with renal failure. Hyperphosphatemia causes tissue deposition of calcium phosphate complexes and the suppression of 1α-hydroxylase, the enzyme responsible for the production of the active vitamin D analog. These factors cause early hypocalcemia. In patients with massive muscle breakdown, significant amounts of potassium are released into the blood. Renal elimination is insufficient if patients have ARF.

Often, hyperkalemia in patients with rhabdomyolysis is life-threatening and requires immediate treatment. Nucleosides are released from disintegrating cell nuclei into the blood and are metabolized in the liver to purines such as xanthine, hypoxanthine and uric acid, the latter of which may contribute to tubular obstruction. The creatinine precursor, creatine, is one of the major components of the muscles where it plays a role in energy transport. It is massively released from non-viable muscle cells and converted into creatinine. It would appear that during rhabdomyolysis, serum creatinine levels should be extremely high, but such a disproportionate increase is not seen, which can be explained by kinetic and mechanistic reasons. Serum creatinine is indeed higher in some patients with rhabdomyolysis, but this can be explained by the fact that patients are younger than those with other causes of ARF of acute renal failure [Byrne, 2004].

Conclusions

The primary management in muscle rhabdomyolysis is to prevent acute kidney damage. The filtration function of the kidneys should be improved by administering a physiological saline solution in order to remove the components of the breakdown of muscle fibers from the body. It is important to avoid solutions containing potassium or lactatin. A solution with approximately 50% sodium can be administered as sodium bicarbonate. This helps to correct induced acidosis by releasing protons from damaged muscles to prevent myoglobin precipitation in the tubules and reduce the risk of hyperkalemia.

Myoglobinuria without kidney damage does not require specific treatment. Rest, hydration and control of urine output are required. Hospital treatment is required if there are signs of developing ARF. A large amount of fluids (up to 10 l), urine alkalinization above pH 6.5 (sodium bicarbonate), electrolyte control and increasing diuresis to at least 300 ml per hour (manitol) in the first 24 hours of the disease prevent kidney damage.

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