

# Exercise-Induced Rhabdomyolysis

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## ABSTRACT

Exercise-induced rhabdomyolysis, or exertional rhabdomyolysis (ER), is a clinical entity typically considered when someone presents with muscle stiffness, swelling, and pain out of proportion to the expected fatigue post exercise. The diagnosis is confirmed by myoglobinuria, and an elevated serum Creatinine Phosphokinase (CPK) level, usually 10 times the normal range. However, an elevation in CPK is seen in most forms of strenuous exercise, up to 20 times the upper normal range. Therefore, there is no definitive pathologic CPK cut-off. Fortunately the dreaded complication of acute renal failure is rare compared to other forms rhabdomyolysis. We review the risks, diagnosis, clinical course and treatment for exercise-induced rhabdomyolysis.

**KEYWORDS:** exertional rhabdomyolysis, CPK, myoglobinuria, acute renal failure

## INTRODUCTION

Rhabdomyolysis (RM) is a condition of striated muscle damage, usually in conjunction with an elevation in creatine phosphokinase (CPK). The mechanism involves either trauma or intracellular depletion of ATP leading to intracellular influx of calcium. This in turn results in the disruption of the cell membrane, and subsequent release of intracellular contents into the plasma and extracellular space. It is this translocation of intracellular debris that can potentially lead to serious complications, most notably acute renal failure (ARF). The incidence of acute renal failure complicating RM ranges from 15-50%. The most common causes of RM with resultant acute renal failure include ischemia, drugs, alcohol and trauma. Melli<sup>1</sup> reported 475 hospitalized patients with RM at John Hopkins. Exogenous toxins, including illicit drugs, alcohol and medications were the most common cause, with an incidence of acute renal failure being 46%.

The incidence of exercise-induced or exertional rhabdomyolysis (ER) in the general public is difficult to define, as many patients probably do not seek medical attention. However, data have been accrued from military recruits undergoing basic training. Wildly ranging rates have been described, due to the varying definitions utilized. The largest data set was by Hill,<sup>2</sup> who reported, in a retrospective review of

574,688 U.S. Army soldiers, 1203 cases of ER or 0.2%. This translates to a yearly rate of 7-8 cases/10,000. Rates were higher men vs. women. Olerud et al,<sup>3</sup> using serum myoglobin as a screening test, diagnosed ER in 40% of military recruits within the first 6 days of basic training.

## DIAGNOSIS

The varying rate of ER is due to the nebulous diagnostic criteria. Clinically it can manifest itself with prolonged muscle swelling and tenderness, lasting several days longer than expected. Ensuing dark urine may develop, signifying myoglobinuria. Elevation of CPK is one of the main serologic criteria to define the entity. However, there is no defining set point in the height of the CPK rise to identify clinically relevant ER. A confounding factor is that CPK elevation after strenuous activity is quite common, with the range being quite variable. Thus, no normal post-exercise CPK value has been established. Studies in male marathoners<sup>4</sup> and triathletes have demonstrated, 24 hours after race completion, CPK elevation in the several thousand range, 10-20 times the upper limit of normal. Of the exercises associated with ER, downhill running and those that induce eccentric (muscle lengthening) contractions tend to be more commonly identified. Examples would include squat thrusts, pushups, and biceps curls. Clarkson<sup>5</sup> measured CPK in 203 healthy, but relatively physically inactive college students after 2 sets of elbow curls with weights for 25 repetitions. Mean CPK rose to a peak of 7713 at day 4, with a range of 50-80,550. The enzyme elevation lasted until day 10 post exercise. No participant developed any medical complications. ER has also been reported in a host of other physical activities including spinning, rock climbing, ice skating, and swimming. A common thread seen in ER is continued exertion beyond the point of fatigue. This is typically seen in a group setting, where peer pressure plays a role, or under the supervision of a demanding personal trainer.

## RISK FACTORS

Asides from the type and duration of exercise, several other risks factors are associated with ER. Studies have shown that at baseline and post exercise, elevations in CPK are greater in men vs. women. Also CPK increments are greater in blacks vs. Caucasians.<sup>2,11</sup> Increased muscle mass is thought to

explain the gender difference.<sup>4</sup> The ethnic difference explanation is more elusive. One entertained mechanism is the prevalence of sickle cell trait, which may lead to an exaggerated rise in post exercise CPK.<sup>13</sup> Another potential risk is any factor that may hamper bodily heat release. Drugs, particularly amphetamines, are implicated, as they cause peripheral vasoconstriction. Concordant with this hypothesis, is the fact that history of heat stroke may also be another predisposing factor. This was noted in a retrospective review by Hill in the military recruits. As a result, rubber suits, used by wrestlers to lose water weight have been banned. If ER is recurrent in an otherwise healthy, young patient, inherited muscle enzyme defects should be considered. The most common include carnitine palmitoyl transferase deficiency, myophosphorylase deficiency (McArdle's disease) and adenosine monophosphate deaminase deficiency.

## COMPLICATIONS

The serious complications of RM include ARF, hyperkalemia, DIC and compartment syndrome. Fortunately, these are all rare with ER. This is most likely due to the fact many of these patients are relatively young and healthy. If acute renal failure develops from ER, full renal recovery is nearly universal. Sinert<sup>6</sup> reported 35 ED admissions for ER with a mean CPK of 40,471. No patient developed acute kidney injury. Hill's<sup>2</sup> data reported an incidence of 8% in the 1203 cases of EH, all of whom recovered renal function.

One question frequently asked is, what level of CPK is associated with kidney injury? Although those who develop renal damage tend to have a higher CPK levels, the correlation between peak of CPK rise and acute renal failure is poor. Some studies have suggested renal injury is associated with CPK in excess of 20,000. However, there are also case reports of it occurring at 5,000.<sup>8</sup> Complicating the issue is that there are frequently other contributing factors to renal damage in those studies. Meijer<sup>7</sup> reported the clinical course of 26 ICU admissions with severe RM, defined as CPK >10,000. The most common causes were ischemic and trauma, none due to exercise. Those who developed acute renal failure had a mean peak CPK of 55,366 vs. 28,643. However, there was substantial overlap between the 2 groups, and no defining level could be ascertained. Therefore, no CPK level has been established in the literature to predict ARF.

ARF from RM is the most serious complication that physicians are attuned to. It was first described in the medical literature in the 1940s by Beall and Bywater.<sup>12</sup> They reported uremic deaths several days following crush injuries due to bombing raids in London. The mechanism of kidney injury is several-fold. Myoglobin, the heme-based oxygen carrying component in muscle is released into the circulation. It is believed to be toxic to the renal tubules. Secondly, there is a period of renal vasoconstriction hampering perfusion.

Lastly, there can be severe third spacing with fluid being sequestered into damaged muscle, leading to an effectively pre-renal condition. Due to the last mechanism, vigorous isotonic intravenous fluids have been the hallmark of preventive therapy. Volumes suggested range from 6-10 liters over the first 24 hours to maintain a urine output of 200-300ml/hour. The earlier the fluid administration, the better, a conclusion Ori Better<sup>9</sup> reported in crush victims from a collapsed building. However, therapy needs to be individualized, with close attention paid to the patient's volume status. IVF administration to the point of overt fluid overload has been associated with increased mortality in ICU patients.

## TREATMENT

The issue of type of intravenous fluid is still debated. Although urinary alkalinization can increase the solubility of myoglobin, the superiority of bicarbonate containing solutions over saline has not been confirmed. The same holds true for mannitol, another agent frequently employed to prevent and treat RM-associated ARF. In a retrospective review of 74 cases of kidney injury due to trauma-induced RM, Brown<sup>8</sup> found no benefit with mannitol or bicarbonate solution. In addition, there is a risk of osmotic induced tubular injury with mannitol administration. A serum osmolar gap >50 can predispose to this untoward complication.

Hypothetically, extracorporeal removal of myoglobin can be beneficial. Due to the size of the heme protein, it is not removed with conventional hemodialysis. However, plasmapheresis<sup>10</sup> can effectively extract the compound from the vascular space. High flux continuous hemofiltration also can remove it as well. Regardless, there are no randomized studies that establish either modality as a preventative measure or treatment for ARF. Thus neither can be recommended.

## SUMMARY

A post-exercise CPK rise is a common phenomenon. The defining line from a normal physiologic response to a disease state is a blurry one. When complications are initially apparent, then the distinction is obvious, but frequently, they are not present. Avoidance of alcohol, amphetamine-based drugs and the gradual increments in exercise intensity are recommended to attenuate ER. One issue is when to admit patients. Acute renal failure is quite rare and when it does occur, it almost always resolves completely. Therefore, in the absence of serious complications, the decision to admit is generally intuition based. CPK tends to peak at day 4, but can remain elevated for 1-2 weeks. If a patient presents without evidence of ARF, it would be unlikely to develop after generous IV isotonic fluid administration. Rate and volume of fluid needs to be individualized and clinically-based.

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