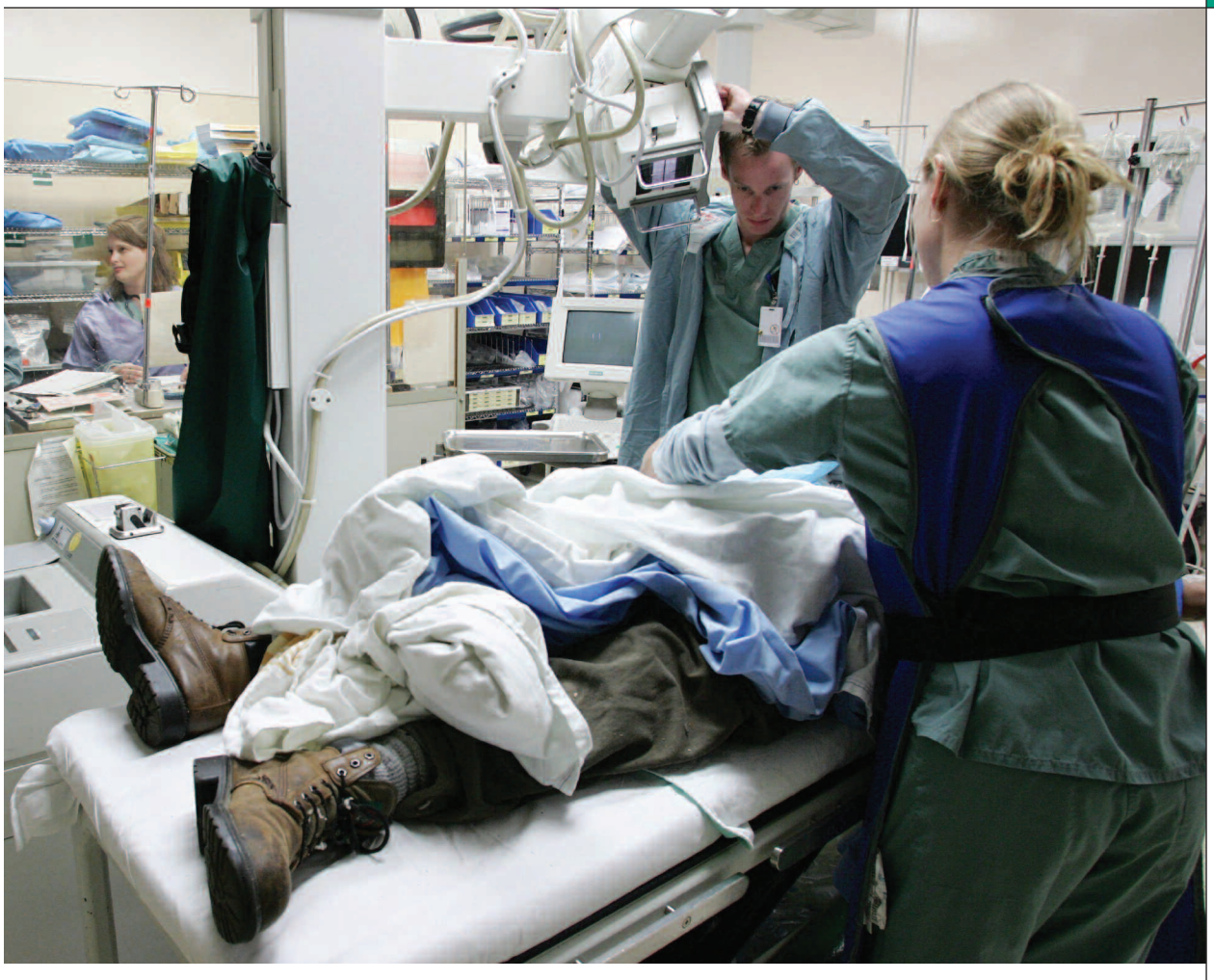

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Crush Injuries:

Pathophysiology and Current Treatment

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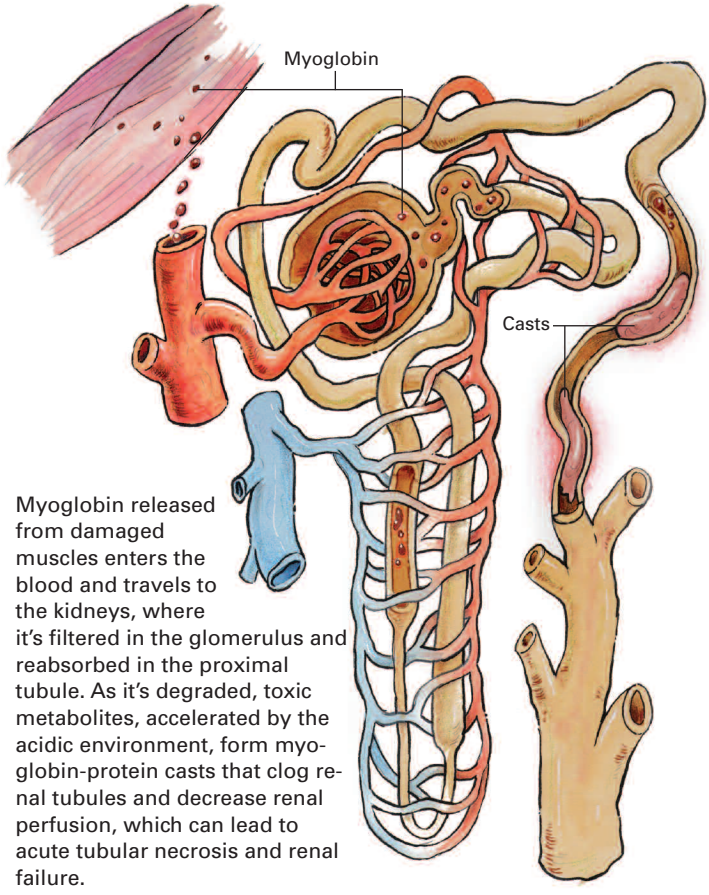
Crush syndrome, also known as traumatic rhabdomyolysis, was first reported in 1910 by German authors who described symptoms including muscle pain, weakness, and brown-colored urine in soldiers rescued after being buried in structural debris.[1] Crush syndrome was not well defined until the 1940s when nephrologists Bywaters and Beal provided descriptions of victims trapped by their extremities during the London Blitz who presented with shock, swollen extremities, tea-colored urine, and subsequent renal failure.[1-4] Rhabdomyolysis often causes myoglobinuric renal failure, electrolyte disturbances, acidemia, and hypovolemia; its symptoms have since become known as crush syndrome. This article reviews the epidemiology, pathophysiology, diagnosis, and early management of crush syndrome.

Epidemiology

Crush injuries may result in permanent disability or death; therefore, early recognition and aggressive treatment are necessary to improve outcomes. There are many known mechanisms inducing rhabdomyolysis including crush injuries,

Rhabdomyolysis



Myoglobin released from damaged muscles enters the blood and travels to the kidneys, where it's filtered in the glomerulus and reabsorbed in the proximal tubule. As it's degraded, toxic metabolites, accelerated by the acidic environment, form myoglobin-protein casts that clog renal tubules and decrease renal perfusion, which can lead to acute tubular necrosis and renal failure.

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electrocution, burns, compartment syndrome, and any other pathology that results in muscle damage. Victims of natural disasters, including earthquakes, are reported as having up to a 20% incidence of crush injuries, as do 40% of those surviving extrication from structures that collapse in both natural and man-made disasters.[2] Crush injures may also be caused by more common events, including vehicular crashes, industrial or mining mishaps, and farming incidents, where extremities become pinned in moving machine parts. The clinician must also be alert to the symptoms of rhabdomyolysis in persons with prolonged seizures, vigorous exercise, or prolonged immobility, and from reactions to medications such as colchicine and the HMG-CoA reductase inhibitors (statins). According to the National Center for Health Statistics,[5] the overall incidence of traumatic rhabdomyolysis is 0.1 per 10,000 population, making it one of the least common traumatic injury patterns. However, if not treated appropriately, it may be lethal. Overall mortality from rhabdomyolysis is about 5%, but varies widely with the precipitating cause.[5]

Pathophysiology

Traumatic rhabdomyolysis, as it pertains to crush syndrome, results when muscle mass is compressed, causing direct injury to muscle fibers. As the tissue is compressed, it is deprived of blood flow and becomes ischemic, eventually leading to cellular death. The time to injury and cell death varies with the crushing force involved; however, skeletal muscle can often tolerate ischemia for up to 2 hours without permanent injury. In the 2- to 4-hour range, some reversible cell damage occurs, and by 6 hours irreversible tissue necrosis generally sets in.[4] In addition to ischemic cell damage, direct injury from the crushing forces causes cell membrane failure and the opening of intracellular sodium and calcium channels. The opening of these channels results in the shift of calcium and sodium into hypoxic cells. This damages myofibril proteins and results in both worsened cell membrane dysfunction and the release of ATP-inhibiting nucleases. The resultant pressure-induced reduction in aerobic metabolism is further compounded by the ischemia of reduced blood flow.

Crush injury also causes hypovolemia by hemorrhagic volume loss and the rapid shift of extracellular volume into the damaged tissues. Acute renal failure (ARF) is caused by hypoperfusion of the kidneys, which normally receive 25% of cardiac output.[6] This hypoperfusion compounds the toxicity caused by cast formation and mechanical blockage of the nephrons by myoglobin, and underscores the importance of early, vigorous volume resuscitation to improve urine flow, which dilutes and clears toxins.

Return of circulation to the injured and ischemic area after rescue also results in injury, as reperfusion leads to increased neutrophil activity and the release of free radicals. Superoxide, the anion form of oxygen (O_2) and hydrogen peroxide (H_2O_2) react to form the hydroxyl radical (OH), which, in a large enough concentration, damages cellular molecules and causes a lipid peroxidation. Lipid peroxidation leads to cell membrane destruction and cell lysis.[7] This damage leads to a further increase in the absorption of fluid, calcium, and sodium into the damaged cells. The amount of fluid that may be rapidly sequestered in the injured muscle can be equal to the extracellular volume of the patient, about 12 liters in a 75-kg adult.[8] This, in part, accounts for

one of the main sequelae of crush syndrome, hypovolemia, which is discussed later in this article.

A second effect from pressure and reperfusion is the release of debris from the damaged cells into the circulation. This debris includes potassium, phosphorus, and myoglobin, the latter is responsible for the ARF that can occur with the syndrome. Myoglobin, an oxygen-binding molecule, contains a heme group and a globin group that disassociate into globin and ferrihemate when released into the circulation, especially in an acidic environment such as that of hypoperfusion. Myoglobin and myoglobin breakdown products, particularly in the presence of acidic urine (pH lower than 5.4), have a toxic effect on the renal tubules and react with the Tamm-Horsfall proteins in the renal tubules to form casts.[8] Recent literature implicates free radical formation as worsening cast-induced renal toxicity.[4]

Another complication of crush injuries is the development of compartment syndrome, which occurs when pressures increase within a fascia-encased region, classically a muscle group or the abdomen. The fascia provides a nonexpandable space, and, as fluid is sequestered, the pressure within the compartment rises. With the rise in pressure, the microvascular circulation is compromised leading to tissue ischemia. The signs and symptoms of compartment syndrome in an extremity include pain out of proportion to the injury or with passive motion, pallor, paresthesia, pulselessness, and paralysis of the affected extremity. Attempts should be made to intervene before there is a loss of pulses, an ominous finding that will almost always reflect irreversible tissue necrosis. Compartment syndrome may also occur in the abdomen. To monitor abdominal compartment syndrome, bladder pressures may be obtained through an indwelling urinary catheter. Pressures higher than 25 mmHg often warrant surgical decompression.

Diagnosis

The release of myoglobin into the circulation should be considered whenever there is significant muscle injury. Normal serum values vary depending on the laboratory results, but are usually less than 85 ng/mL. With significant muscle damage, it is possible for the value to rise astronomically, perhaps more than 150,000 ng/mL.[8] The serum myoglobin levels may be initially higher in comparison to urine values, but as myoglobin is cleared from the body, these values will flip and the amount of myoglobin in the urine will be higher. Tracking both serum and urine myoglobin values, although sometimes cost prohibitive, is the best way to follow progression and resolution of crush injury.

A simple but rapid test for rhabdomyolysis can be done with a standard urine dipstick. The heme portion of myoglobin causes a positive reading for blood on the test strip, and heme-positive urine in the absence of any red blood cells on microscopic examination suggests myoglobinuria. However, dipstick findings are positive in only about one-half of patients with rhabdomyolysis and the findings are sometimes intermittent. Accordingly, a normal urine dipstick does not rule out the condition and a laboratory evaluation for myoglobin should be performed in patients suspected of having crush syndrome.

Creatine phosphokinase (CPK) is another marker of muscle damage and laboratory testing is commonly available. CPK is released with any muscle breakdown. With rhabdomyolysis, the levels are tremendously high, often in excess of 30,000 units/liter and correlate with the amount of muscle damaged.[3,8] Although crush injury can produce spectacularly high CPK values, the incidence of renal failure becomes significant at a threshold of only 5,000 units/liter. This level should prompt aggressive evaluation and intervention.[9] As the half-life of CPK is about 1.5 days and that of myoglobin is about 3 hours, tracking both CPK and myoglobin values is beneficial when trying to guide treatment decisions.

Subsequent treatment should be aimed at restoring end-organ perfusion and preventing renal failure by volume expansion.

Management

The most important prehospital treatment goal should be the removal of the crushing forces. Initial treatment, whether out-of-hospital or in-hospital, begins with the initiation of intravenous hydration. Subsequent treatment should be aimed at restoring end-organ perfusion and preventing renal failure by volume expansion. Volume expansion also aids in correcting the acidemia caused by hypoperfusion. Vascular access should be established with two large-bore peripheral catheters, central venous line, or intraosseous routes. Initial fluid therapy should be directed at correcting tachycardia or hypotension with rapid volume expansion using isotonic sodium chloride solution or lactated Ringers solution and then slowing to a more controlled rate of 1 to 1.5 liters/hr as a continuous infusion.[1, 4, 8, 10, 11] The ultimate goal of therapy is aimed at achieving a urine output of 300 to 400 mL/hr.[4] This aggressive volume expansion can prevent the rapid death, sometimes known as rescue death, which often accompanies removal from the crushing forces

and reperfusion of ischemic tissue.

In addition to crystalloid replacement, blood or blood products may also be needed on the basis of the specific situation. Crush injuries may result in coagulopathies, necessitating the transfusion of fresh frozen plasma or platelets. Should there be ongoing active bleeding or a marked reduction in hemoglobin to 8 grams/dL or less in healthy individuals, or below 10 grams/dL in persons with underlying cardiac, pulmonary, or cerebrovascular disease, a transfusion of packed red blood cells may be needed to optimize oxygen transport. Careful attention must be paid to ensure that renal function is sufficient to provide adequate urine output and prevent pulmonary congestion from volume replacement. This is especially important if resuscitation is started more than 6 hours postinjury because renal damage may have already taken place.

Although difficult to achieve, alkalinization of the urine may be beneficial in preventing renal failure and can be started with initial volume resuscitation. The breakdown of myoglobin results in a nephropathy, causing sloughing of the tubular epithelium and the formation of casts that obstruct blood flow through the kidneys.[12] In alkalotic urine, myoglobin breakdown has a less toxic effect. Urine alkalinization may be accomplished by adding 50 mEq of sodium bicarbonate to each liter of maintenance fluid. The therapeutic endpoint is a urine with a pH of 6 to 7; the normal value is between 4.6 and 8.[1, 2, 8, 11] Should systemic alkalosis occur with a pH of more than 7.5, acetazolamide, a carbonic anhydrase inhibitor that promotes metabolic acidosis by inhibiting carbonic anhydrase in the kidneys, may be indicated.

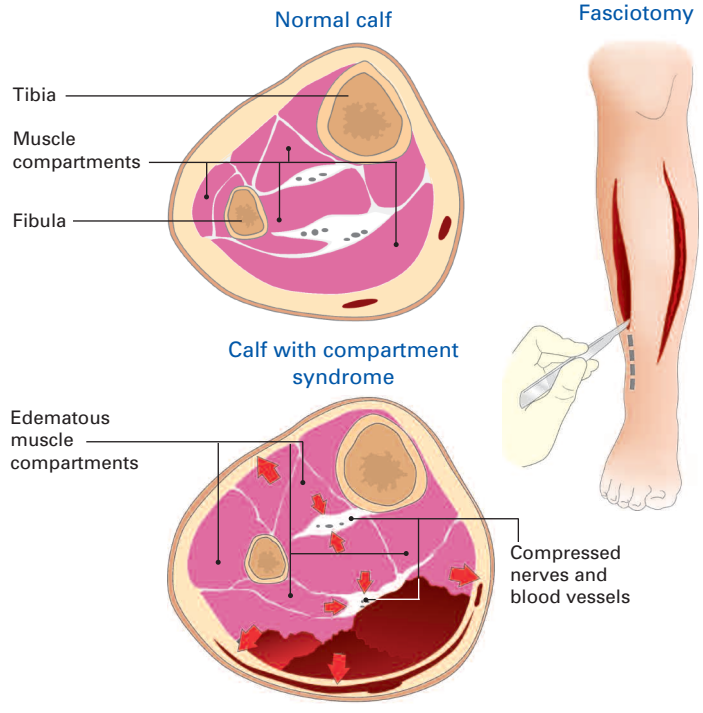
Once adequate urine output is accomplished, the "push" provided by volume expanders may be augmented by a "pull" from forced diuresis with a 20% mannitol solution, with an initial dose of 25 grams followed by a 5 grams/hr infusion.[8] The osmotic diuretic effects of the mannitol enhance urine output and facilitate the clearance of myoglobin. Mannitol also reduces compartment pressures by mobilizing fluid from the extravascular to intravascular spaces, which may facilitate tissue perfusion and act as a free radical scavenger, protecting the kidneys from injuries incurred by oxidants.[4] Whenever mannitol is administered, a chemistry panel and serum osmolality should be followed to monitor for electrolyte disturbances, particularly hypokalemia and a rise in osmolality that would indicate dehydration. Once diuresis has been initiated, potassium levels may fall in spite of the massive release from damaged muscle tissue and potassium repletion may be paradoxically required. Loop diuretics such as furosemide may acidify the urine and should be avoided.

A recent study, however, showed no benefit of the addition of either sodium bicarbonate or mannitol to the treatment regimens of patients with posttraumatic rhabdomyolysis and CPK levels of 5,000 units/liter or higher. The use of these therapies offered no change in overall rates of renal failure, dialysis, or mortality.[9] The use of both therapies remains controversial and additional research is warranted to guide practice.

Patients who do not respond to hydration and forced diuresis by producing more than 400 mL of urine per day will almost certainly require hemodialysis, as will most patients who present with an initial serum creatinine of more than 1.7 mg/dL.[3,11,13] Up to one-third of all patients with rhabdomyolysis will go on to require hemodialysis so long it is safe and possible, patients with significant crush injuries should be triaged directly to centers with onsite, around-the-clock, hemodialysis capabilities. There is research supporting serum CO_2, blood urea nitrogen, calcium, creatinine, and a urine dip for blood as the most valuable predictors for the development of ARF or the need for hemodialysis.

What Happens in Compartment Syndrome?

These illustrations show a cross-section of a normal calf and a cross-section of a calf with compartment syndrome. Compartment pressures over 30 mmHg often require surgical decompression with a fasciotomy.



Treatment of Hyperkalemia

Membrane antagonism	Calcium directly antagonizes the effects of potassium. Calcium chloride is the preferred choice over calcium gluconate if there is circulatory compromise, as 10 mL of a 10% solution (1 gram) contains three times more elemental calcium than the same volume of calcium gluconate.
Cellular shift	Treatment with insulin and dextrose forces potassium into the cells and may decrease serum potassium by 1 mEq/L. Administer 10 units of regular insulin I.V. and 25 grams dextrose I.V.
Exchange resin	Polystyrene sulfonate (Kayexalate) is an exchange resin that enhances potassium clearance across the gastrointestinal tract mucosa. Administer 30 grams P.O.
Albuterol	Although no longer widely utilized for the reduction of potassium, albuterol as a continuous nebulizer may be used to lower serum levels by stimulating intracellular uptake of potassium.
Hemodialysis	Removes potassium from blood.

As with any volume-dependent patient, continuous venovenous hemofiltration may be the best dialysis option, as it requires the smallest amount of volume to be removed from the patient.[3,11,13] Potassium is found in high quantity in muscle tissue, and reperfusion of damaged muscle tissue releases it into the circulation. The risk for significant hyperkalemia is compounded by any renal impairment that might occur concomitantly with the rhabdomyolysis. Persons suffering with crush injuries should have continuous cardiac monitoring and electrocardiogaphic evaluation for the signs of hyperkalemia such as tall-peaked T waves, a lengthening PR interval, followed by a loss of P waves, and ultimately a widening of the QRS complex into a sine wave, which is a precursor to asystole.[14] Standard treatment modalities such as calcium, insulin, dextrose, and an exchange resin may temporize the situation; however, dialysis may be needed for definitive treatment (see Table: "Treatment of Hyperkalemia").

Patients should not be empirically treated with calcium in an effort to blunt the effects of potential hyperkalemia. Treatment should be based on clinical findings such as anxiety, numbness and tingling, nausea/vomiting, electrocardiogram abnormalities suggestive of elevated potassium levels, or actual laboratory values. A relative hypocalcemia exists because the body's calcium stores are absorbed by hypoxic tissues due to reperfusion and because of a state of hyperphosphatemia resulting from phosphorus loss from damaged cells. Injudicious administration of calcium intravenously leads to more calcium absorption into the damaged cells, aggravating rhabdomyolysis and resulting in metastatic calcification that, with time, can lead to tissue calcification or a deleterious hypercalcemia.[2] Compartment syndrome could be diagnosed by direct measurement of pressures within the fascia. This is achieved by introducing a transduced needle into the compartment space. Pressures normally lie in a range from 0 to 15 mmHg, and pressures of more than 30 mmHg often require surgical decompression with a fasciotomy. Pressures in the abdomen can be determined by measuring the pressure within the bladder through an indwelling urinary catheter. Patients with bladder pressures of more than 25 mmHg should be considered potential candidates for surgical decompression if there is clinical evidence of organ dysfunction as well. Higher diastolic blood pressures allow perfusion, and another course followed is to treat when any compartment pressures rise to within 20 points of diastolic blood pressure.[4]

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