DISEASE OF THE MONTH

Eberhard Ritz, Feature Editor

J Am Soc Nephrol 11: 1553–1561, 2000

Rhabdomyolysis

RAYMOND VANHOLDER,* MEHMET SÜKRÜ SEVER,† EKREM EREK,‡ and NORBERT LAMEIRE§

**Renal Division, University Hospital, Gent, Belgium (Renal Disaster Relief Task Force of the International Society of Nephrology); †Istanbul Medical Faculty, Çapa Campus, Istanbul, Turkey (local coordinator for the Renal Disaster Relief Task Force); 3‡Istanbul Medical Faculty, Cerrahpasha Campus, Istanbul, Turkey (President of the Turkish Society of Nephrology); and §Renal Division, University Hospital, Gent, Belgium (coordinator for the European Section of the Renal Disaster Relief Task Force).*

The term rhabdomyolysis refers to disintegration of striated muscle, which results in the release of muscular cell constituents into the extracellular fluid and the circulation. One of the key compounds released is myoglobin, an 18,800-Dalton oxygen carrier. It resembles hemoglobin, but contains only one heme moiety. Normally, myoglobin is loosely bound to plasma globulins and only small amounts reach the urine. When massive amounts of myoglobin are released, the binding capacity of the plasma protein is exceeded. Myoglobin is then filtered by the glomeruli and reaches the tubules, where it may cause obstruction and renal dysfunction (1).

The degree of rhabdomyolysis that can manifest ranges from a subclinical rise of creatine kinase (CK) to a medical emergency comprising interstitial and muscle cell edema, contraction of intravascular volume, and pigment-induced acute renal failure (ARF). Today, rhabdomyolysis is one of the leading causes of ARF (1,2). The prognosis of rhabdomyolysis-associated ARF is relatively benign (3).

One major cause of rhabdomyolysis is the crush syndrome, *i.e.*, myolysis is linked to traumatic compression of muscle followed by reperfusion, as is frequently seen in accidents or disasters. Muscular trauma, however, does not always lead to rhabdomyolysis, not all rhabdomyolysis leads to ARF, and not all ARF related to crush is attributable to rhabdomyolysis. Alternative causes of ARF in rhabdomyolysis may include dehydration, sepsis, and drug nephrotoxicity. Most cases of rhabdomyolysis in peacetime are nontraumatic; they are most frequently the consequence of seizures, alcohol abuse, or compression as a result of coma (see below) (4).

Historical Notes

Rhabdomyolysis was observed in ancient times (5). The Old Testament refers to a plague suffered by the Israelites during their exodus from Egypt after abundant consumption of quail (Book of Numbers 11:31–35). Myolysis after the consumption of quail is well known in the Mediterranean region. It is the result of intoxication by hemlock herbs, which are consumed by quails during their spring migration (6). Remarkably, indirect evidence substantiates that this biblical episode occurred in springtime (5).

In modern times, the first cases of crush syndrome and ARF were reported during the Sicilian earthquake in Messina in 1908 and in the German military medical literature during World War I (7). The latter concerned cases of rhabdomyolysis observed after soldiers had been buried in trenches.

In modern English medical literature, the authors of the first detailed report of ARF related to the crush syndrome were Bywaters and Beall. They observed the condition in four victims of the bombing of London during the Battle of Britain in 1940 (7). The authors pointed to the link between rhabdomyolysis and renal failure. The role of myoglobin was later classified in greater detail in an experimental publication (8). It was only decades later, in the early 1970s, that nontraumatic causes of rhabdomyolysis were recognized and identified as a potential cause of ARF (9,10).

Etiology

It is beyond the scope of this review to discuss the many conditions in which rhabdomyolysis may occur, but we shall summarize the most frequent ones (Table 1).

Trauma and Compression

Traumatic rhabdomyolysis is mainly the result of traffic or occupational accidents. Compression of the muscles may also be induced by torture, abuse, or long-term confinement in the same position (orthopedic problems; surgical interventions necessitating specific positions for a long time; psychiatric conditions; coma).

Occlusion of the Muscular Vessels

Thrombosis, embolism, or clamping of vessels during surgery may all result in muscle cell necrosis if oxygen deprivation is maintained for prolonged periods (11). ARF occurs only if a critical mass of muscle has become necrotic, *e.g.*, after total

Correspondence to Dr. Raymond Vanholder, Renal Division, Department of Internal Medicine, University Hospital Gent, De Pintelaan 185, B9000, Gent, Belgium. Phone: +32 9 2404525; Fax: +32 9 2404599; E-mail: raymond.vanholder@rug.ac.be

1046-6673/1108-1553

Journal of the American Society of Nephrology

Table 1. Etiology of rhabdomyolysis

- Physical causes
  - trauma and compression
    - traffic or working accidents
    - disasters
    - torture
    - abuse
    - long-term confinement to the same position
  - occlusion or hypoperfusion of the muscular vessels
    - thrombosis
    - embolism
    - vessel clamping
    - shock
  - strainful exercise of muscles
    - exercise
    - epilepsy
    - psychiatric agitation
    - delirium tremens
    - tetanus
    - amphetamine overdose
    - ecstasy
    - status asthmaticus
  - electrical current
    - high-voltage electrical injury
    - lightning
    - cardioversion
  - hyperthermia
    - exercise
    - high ambient temperatures
    - sepsis
    - neuroleptic malignant syndrome
    - malignant hyperthermia
- Nonphysical causes
  - metabolic myopathies
    - McArdle disease
    - mitochondrial respiratory chain enzyme deficiencies
    - carnitine palmitoyl transferase deficiency
    - myoadenylate deaminase deficiency
    - phosphofructokinase deficiency
  - drugs and toxins
    - regular and illegal drugs (see Table 2)
    - toxins
      - snake and insect venoms
      - buffalo fish (United States), burbot (Northern Europe)—Haff disease
  - infections
    - local infection with muscular invasion (pyomyositis)
    - metastatic infection (sepsis)
    - systemic effects
      - toxic shock syndrome
      - *Legionella*
      - tularemia
      - *Salmonella*
      - falciparum malaria
      - influenza
      - HIV
      - herpes viruses
      - coxsakievirus
  - electrolyte abnormalities
    - hypokalemia
    - hypocalcemia
    - hypophosphatemia
    - hyponatremia
    - hypernatremia
    - hyperosmotic conditions
  - endocrine disorders
    - hypothyroidism
    - diabetic coma, related to electrolyte disturbances
  - polymyositis/dermatomyositis

vascular occlusion involving at least one limb, after multiple diffuse emboli, or during generalized shock.

Strainful Exercise of Muscles

Strenuous muscular exercise may cause myolysis, especially in untrained subjects or in individuals exercising under extremely hot or humid conditions (12,13). Muscle necrosis more frequently occurs after downhill walking than after uphill climbing. The combination of muscular exertion, hypoxemia, and corticosteroid-induced myopathy may cause myolysis in patients with status asthmaticus (14). Because K^+ is essential for vasodilation of the microvasculature of the muscles, exercise will cause more rapid muscle ischemia in hypokalemic subjects (15).

Electrical Current

High-voltage electrical injury and lightning strikes cause rhabdomyolysis in at least 10% of the subjects surviving the primary accident, even if the wounds of the site of entry are small (16). Myolysis is attributable to thermal injury, or to electrical disruption of sarcolemmal membranes. The latter results in pore formation, loss of barrier function, and massive calcium influx (17).

Hyperthermia

An excessive body temperature may result in muscle damage. One cause of hyperthermia-associated rhabdomyolysis is the neuroleptic malignant syndrome, which is characterized by high fever in patients treated with phenothiazides or haloperidol (18). Another potential cause is malignant hyperthermia, an inheritable condition that is characterized by a rapid rise of body temperature (1°C/5 min), typically after anesthesia with halogenated hydrocarbons or succinylcholine (19). As a result of excessive sweating, these patients often also have hypokalemia, which may aggravate damage to the muscles.

Metabolic Myopathies

Exceptional causes of rhabdomyolysis are inherited diseases that have in common failure of energy delivery to the muscles because of defects in glucose, glycogen, lipid, or nucleoside metabolism. These disorders usually start during childhood and should be suspected if muscular weakness or myoglobinuria recur frequently, or appear in association with events that are unlikely to precipitate rhabdomyolysis in healthy subjects (20). In most cases, the final common pathway leading to muscle cell disintegration is deficient delivery of adenosine triphosphate (ATP), so that cell integrity cannot be maintained (21). Viral infection, exertion, or fasting are aggravating factors. In separate reports, Poels and Gabreëls and Brumback *et al.* have provided a detailed description of the relevant metabolic defects (22,23).

Drugs and Toxins

Regular and illegal drugs that cause rhabdomyolysis, together with their mechanisms of action, are listed in Table 2. Perhaps the most frequent cause of drug-induced rhabdomyolysis today is the administration of HMG-CoA reductase inhib-

Table 2. Main drugs responsible for rhabdomyolysis, together with the mechanism causing ARF[a]

Agent	Compression	Myotoxicity	Hypokalemia	Other
Alcohol	+	+	+	Hypophosphatemia
Amphetamine				Agitation
Amphotericin B			+	
Antimalarials		+		
Carbon monoxide	+			Energy deficiency, hypoxia
CNS depressants	+			
Cocaine				Hyperthermia, agitation
Colchicine		+		
Corticosteroids		+		
Diuretics			+	
Ecstasy				Agitation
Fibrates		+		
HMG-CoA reductase inhibitors		+		
Heroin	+	+		
Isoniazid		+		
Laxatives			+	
Licorice			+	
Narcotics	+			
Phencyclidine (PCP)	+			Agitation, seizures
Zidovudine		+		

[a] ARF, acute renal failure; CNS, central nervous system.

itors. Immediate withdrawal of these drugs is mandatory if patients complain of muscle problems or if CK rises to more than three times above normal levels. The risk of drug-induced muscle disease is aggravated by simultaneous administration of danazol, nicotinic acid, cyclosporine, itraconazole, or erythromycin. The combination of HMG-CoA reductase inhibitors with gemfibrozil also carries a high risk of myotoxicity (24). Finally, fibrates alone may cause myotoxicity, particularly in patients with renal failure, because most fibrates accumulate when GFR is decreased.

In patients with acute or chronic alcohol intoxication, muscle dysfunction is attributable to a combination of immobilization, hypokalemia, hypophosphatemia, agitation, and/or direct myotoxicity. Such a combination of etiologic factors is also seen in patients treated with psychotropic drugs, or in whom aggression, restraint, intramuscular injections, and/or extrapyramidal effects may act in concert to cause muscle dysfunction (25). Rhabdomyolysis as a result of exposure to toxins is seen not only after ingestion of quails, but also after eating of certain fish species (Haff disease) (26) or after contact with several snake and insect venoms (*e.g.*, hornet and spider).

Infections

Locally invasive infection of muscle (pyomyositis), diffuse metastatic infection of muscles during septicemia, and infection with microbes causing toxic shock syndrome may result in extensive muscle necrosis.

Electrolyte Abnormalities

Hypokalemia, hypocalcemia, hypophosphatemia, hyponatremia, and, particularly, hypernatremia and hyperosmotic conditions all have been associated with rhabdomyolysis. The myotoxicity of alcohol is related in part to electrolyte abnormalities, *i.e.*, hypophosphatemia or hypokalemia (27), but malnutrition and severe illness also may cause electrolyte disturbances that induce rhabdomyolysis. Hypokalemia and hypophosphatemia disappear after overt myonecrosis and renal failure have developed; hence, their causative role is often overlooked.

Pathophysiology of Myolysis

Changes in Cellular Metabolism

Stretching or exhaustive work of muscle cells increases sarcoplasmic influx of sodium, chloride, and water, which results in cell swelling and autodestruction (22). Calcium enters the cell, in exchange for intracellular sodium. Large quantities of free calcium ions trigger persistent contraction, resulting in energy depletion and cell death (23). In addition, calcium activates phospholipase A_2, as well as various vasoactive molecules and proteases. Furthermore, it leads to the production of free oxygen radicals (1). Damaged muscle is invaded by activated neutrophils that amplify the damage by releasing proteases and free radicals (16). The result is an inflammatory, self-sustaining myolytic reaction, rather than pure necrosis.

Reperfusion Injury

In ischemic tissue injury (*e.g.*, myocardial infarction, acute renal failure), most of the damage is not inflicted during the period of ischemia, but after the blood flow into the damaged tissue is restored (reperfusion injury). Leukocytes migrate into the damaged tissue only after reperfusion has started, and production of free radicals starts only when oxygen is amply

available. A similar mechanism is at work in both traumatic and nontraumatic muscular damage (28).

In the case of traumatic rhabdomyolysis, the muscles are initially compressed and ischemic, and muscle dysfunction starts to develop only when the patient is evacuated, *i.e.*, when perfusion of the damaged muscles is restored. This is the main reason that Better and Stein proposed starting infusion of large amounts of fluid before victims of trauma are extricated (29).

Compartment Syndrome

Most striated muscles are contained within rigid compartments formed by fasciae, bones, and other structures. If the energy-dependent transcellular pump systems fail in the traumatized tissue, the muscle cells swell. As a result, intracompartmental pressure rises and may occasionally reach excessive values. High intracompartmental pressure provokes additional damage and necrosis. Because such compartments are noncommunicating, closed systems, the only way to decrease the pressure is to decompress the fascial system surgically by fasciotomy. Not all investigators are enthusiastic about early fasciotomy, because the procedure may create a potential source of infection (29). On the other hand, prolonged pressure may provoke irreversible paralytic damage to the peripheral nerves. It is generally accepted that compartment pressures $>$30 mmHg produce clinically significant muscle ischemia. In hypotensive patients, even lower compartment pressures will cause perfusion problems.

The measurement of intramuscular pressure provides an objective parameter for the decision to perform fasciotomy. In nonhypotensive patients, this should be done when the intramuscular pressure exceeds 50 mmHg or if pressure values between 30 and 50 mmHg show no tendency to decrease after a maximum of 6 h.

Metabolic Derangements during the Course of Rhabdomyolysis

Release of constituents of necrotic muscle results in altered plasma concentrations of several anorganic and organic compounds, which are responsible for toxic and sometimes life-threatening complications (30). The accumulation of these compounds is aggravated by the simultaneous development of renal failure.

Necrosis of the muscles, together with inflammation, results in the accumulation of substantial amounts of fluid in the affected limbs (up to 10 L per limb). Unless large amounts of volume are administered, shock, hypernatremia, and deterioration of renal function will supervene. If muscles recover faster than the kidneys, fluid is released into the circulation at a later stage. Delayed renal elimination may then result in expansion of the extracellular and plasma volume.

At an early stage, dehydration causes *hyperalbuminemia*, whereas later malnutrition, inflammation, capillary leak, and fluid overload cause *hypoalbuminemia*. Changes in serum albumin may result in the misinterpretation of total plasma calcium concentrations.

Release of organic acids from dying muscle cells provokes high anion gap *acidosis* (4). In particular, hypoxic muscles release lactic acid into the circulation; its removal by the liver is inadequate if the patient is hypovolemic. Acidosis will have a deleterious effect on numerous metabolic functions and will enhance the hyperkalemia. The lower urinary pH and intratubular acidosis will facilitate intratubular precipitation of myoglobin and uric acid.

During the early stages of rhabdomyolysis, calcium accumulates in the muscles. Sometimes massive calcification of necrotic muscles or even heterotopic ossification is seen (31,32). In the presence of hyperkalemia, severe *hypocalcemia* may lead to cardiac arrhythmia, muscular contraction, or seizures. The latter damage the muscles even further. Remarkably, some of the patients with rhabdomyolysis do not show hypocalcemia (4). During later stages of the disease, the accumulated calcium is released from the storage sites. This is often associated with hyperparathyroidism and hypervitaminosis D (33), and overt hypercalcemia. However, the hyperparathyroidism and hypervitaminosis D are not seen in all cases (34). Hypercalcemia occurs more frequently if calcium has been supplemented in the hypocalcemic phase.

Phosphorus is released from damaged muscle and accumulates in patients with renal insufficiency. Hyperphosphatemia causes tissular deposition of calcium-phosphate complexes in tissues and suppression of 1α-hydroxylase, the enzyme responsible for the production of the active vitamin D analogue calcitriol. All of these factors together further contribute to the early hypocalcemia.

In patients with massive breakdown of muscles, substantial amounts of potassium are released into the blood. Elimination via the kidneys fails if patients have ARF. Frequently, *hyperkalemia* in patients with rhabdomyolysis is life-threatening, requiring immediate treatment. In nontraumatic rhabdomyolysis, hyperkalemia is not consistently present at the time of admission (4).

Nucleosides are released from disintegrating cell nuclei into the blood and metabolized in the liver to purines such as xanthine, hypoxanthine, and *uric acid*, among which the latter may contribute to tubular obstruction.

The precursor of *creatinine*, creatine, is one of the main constituents of muscle, where it plays a role in energy delivery. It is massively released from nonviable muscle cells and transformed into creatinine. It has been postulated that in rhabdomyolysis, serum creatinine levels should be exceedingly high (9), but such a disproportionate rise is not seen, which may be explained by kinetic and mechanistic considerations (35). Serum creatinines are indeed higher in some patients with rhabdomyolysis, but this may be explained by the fact that those patients are younger than those with other causes of ARF (3).

Pathophysiology of ARF

The pathophysiology of myoglobinuric ARF has been studied extensively in the animal model of glycerol-induced ARF. The main pathophysiologic mechanisms are renal vasoconstriction, intraluminal cast formation, and direct heme-protein-induced cytotoxicity (1). Myoglobin is easily filtered through the glomerular basement membrane. Water is progressively

reabsorbed in the tubules, and the concentration of myoglobin rises proportionally, until it precipitates and causes obstructive cast formation. Dehydration and renal vasoconstriction, which decrease tubular flow and enhance water reabsorption, favor this process (1) (Figure 1). The high rates of generation and urinary excretion of uric acid further contribute to tubular obstruction by uric acid casts. Another factor favoring precipitation of myoglobin and uric acid is a low pH of tubular urine, which is common because of underlying acidosis. The degradation of intratubular myoglobin results in the release of free iron, which catalyzes free radical production and further enhances ischemic damage (1). Even without invoking release of free iron, the heme center of myoglobin will initiate lipid peroxidation and renal injury (36). Alkaline conditions prevent this effect by stabilizing the reactive ferryl myoglobin complex.

Gastrointestinal ischemia is responsible for absorption of endotoxin and release of cytokines, which amplify the inflammatory reaction and cause hemodynamic instability.

Diagnosis and Differential Diagnosis

Myoglobinemia and Myoglobinuria

Myoglobinuria does not occur without rhabdomyolysis, but rhabdomyolysis not necessarily results in visible myoglobinuria. Myoglobin causes discoloration of the urine but not of the plasma. Urinary myoglobin provokes a typical reddish-brown (port-wine-like) color, even in the absence of hematuria (Table 3). The kidneys and urinary tract may have been damaged by trauma, however, so the presence of hematuria in posttraumatic cases does not absolutely exclude the presence of myoglobinuria. Myoglobin is rapidly and unpredictably eliminated by hepatic metabolism. Therefore, tests for myoglobin in plasma or urine are not a sensitive diagnostic procedure.

Red discoloration of the urine when erythrocytes cannot be detected by microscopy must be due to hemoglobinuria or myoglobinuria (Table 4), unless the color of the urine is due to drugs or metabolites (Table 3).

Hemoglobin is structurally and functionally related to myoglobin. Although the molecular weight of hemoglobin (64,600 Daltons) is much higher than that of myoglobin (18,800 Daltons), hemoglobin is still able to cross the glomerular barrier and induce ARF. In patients with hemoglobinuria, but not in patients with myoglobinuria, the plasma will be discolored as well. It is perhaps important to remember that the urinary benzidine dipstick does not differentiate between myoglobin, hemoglobin, and red blood cells.

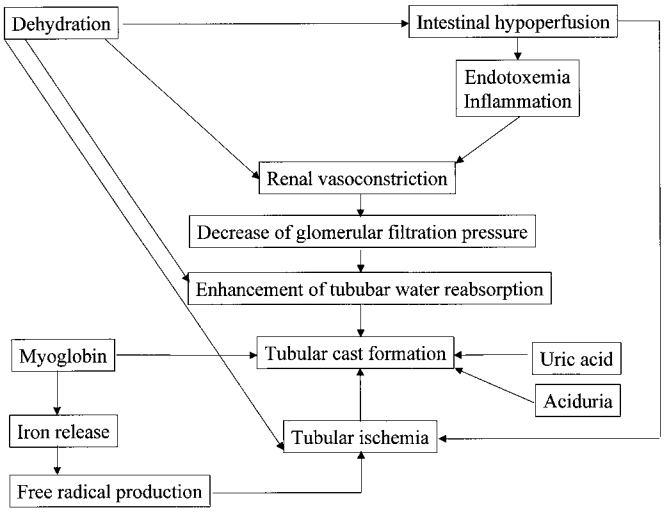

Figure 1. Pathophysiology of acute renal failure in rhabdomyolysis.

Table 3. Causes of reddish-brown discoloration of the urine

Myoglobinuria
rhabdomyolysis
traumatic
nontraumatic
Hemoglobinuria
hemolysis
mechanical damage
immunologic damage
structural fragility of erythrocytes
microangiopathy
Hematuria
renal causes
postrenal causes
External factors
red beets
drugs
vitamin B12
rifampicin
phenolphthalein
phenytoin
metabolites
bilirubin
porphyrin

Creatine Kinase

The enzyme CK is ubiquitously present in striated muscle. When muscle cells disintegrate, CK is released into the bloodstream. Several subtypes of CK exist; some of them are found in striated muscle (CKMM), others in cardiac muscle (CKMB). During rhabdomyolysis, extreme quantities of CKMM are released and peak concentrations of 100,000 IU/ml or more are not unusual. Because overall degradation and removal are slow, the concentration of CK remains elevated much longer and in a more consistent manner than that of myoglobin. Consequently, CK is more reliable than myoglobin in assessing the presence and intensity of damage to the muscles.

Prevention and Treatment

The primary therapeutic goal is to prevent the factors that cause ARF, *i.e.* volume depletion, tubular obstruction, aciduria, and free radical release. The ideal fluid regimen for patients with rhabdomyolysis consists of half isotonic saline (0.45%, or 77 mmol/L sodium), to which 75 mmol/L sodium bicarbonate is added. This combination may be complemented by 10 ml/h of mannitol 15%, if sufficient urinary flow is still present

Table 4. Characteristics of urine and plasma in the different conditions that may cause red discoloration of the urine[a]

Characteristic	Rhabdomyolysis	Hemolysis	Hematuria
Red discoloration plasma	−	+	−
Positive benzidine dipstick	+	+	+
Presence of erythrocytes by urine microscopy	−	−	+
Elevated CK concentration in the blood	+	−	−

[a] CK, creatine kinase.

(Table 5). Once overt renal failure has developed, the only reliable therapeutic modality is extracorporeal blood purification.

Supportive Treatment

Hypovolemia may result from sequestration of water by muscles and must be prevented by the aggressive administration of intravenous fluids (29). To obtain volume equilibrium, the amount of fluid required is as high as 10 L or more per day. In cases in which muscles are compressed as a result of trauma, it is important to start administration of fluid before the victim is extricated from under the rubble (30). Potassium- or lactate-containing solutions should be avoided.

Approximately 50% of the sodium can be administered as sodium bicarbonate. This helps to correct the acidosis induced by the release of protons from damaged muscles, to prevent precipitation of myoglobin in the tubules, and to reduce the risk of hyperkalemia. It should be mentioned that alkaline rehydration was recommended already during World War II, as noted in the seminal paper of Bywaters and Beall (7). The only drawback of bicarbonate administration is the decrease of serum ionized calcium.

The addition of mannitol to the fluid regimen serves several purposes: (*1*) mannitol increases renal blood flow and GFR; (*2*) mannitol is an osmotic agent that attracts fluid from the interstitial compartment, thus counterbalancing hypovolemia and reducing muscular swelling and nerve compression; (*3*) mannitol is an osmotic diuretic that increases urinary flow and prevents obstructive myoglobin casts; and (*4*) mannitol scavenges free radicals. Loop diuretics (furosemide, bumetanide, and torsemide) increase tubular flow and decrease the risk of precipitation of myoglobin, while simultaneously acidifying urine and increasing calcium losses.

Table 5. Fluid administration strategy in patients with impending or ongoing traumatic rhabdomyolysis

- Find a vein in arm or leg even if the patient is still trapped
- Administer fluid as early as possible: start with 1 L before extrication
- Preferable fluid combination (for 2 L)
  1 L of isotonic saline
  1 L of glucose 5% + 100 mmol bicarbonate
- Administer at least 3 to 6 L/d (in emergencies when supervision is not guaranteed) or up to 10 L/d or more if continuous supervision is available
- Add 10 ml of mannitol per hour if urine output is greater than 20 ml/h

Allopurinol may be useful because it reduces the production of uric acid and also acts as a free radical scavenger. Another purine analogue, pentoxyfilline, has been considered in the management of rhabdomyolysis because of its capacity to enhance capillary flow and decrease neutrophil adhesion and cytokine release.

An important therapeutic goal is control of hyperkalemia. Measures that cause a shift of potassium from the extracellular to the intracellular compartment (hypertonic glucose, bicarbonate) have only a temporary effect. If renal function does not recover, those measures should be followed by more definite strategies, such as administration of intestinal potassium binders or dialysis. Calcium carbonate and calcium kayexalate should be used with caution, because they enhance the risk of intramuscular calcium deposition. If necessary, dialysis is indicated, not only in patients with overt hyperkalemia, but also in patients in whom serum potassium rises fast.

Although hypocalcemia is a common complication in the initial phase of rhabdomyolysis, it usually does not require correction, particularly because this would increase the risk of intramuscular calcium deposition. Indications for the correction of hypocalcemia are impending seizures, however.

Extracorporeal Blood Purification

Once acute renal failure has been established, or severe hyperkalemia and acidosis are present, the patient requires dialysis. Fluid overload is a rare indication to start dialysis, because patients tend to be dehydrated due to massive fluid accumulation in the damaged muscle. Hemodialysis has several advantages in these severely catabolic patients: (*1*) it provides efficient removal of solutes, including potassium, phosphate, and protons; (*2*) it creates the possibility of dialyzing without anticoagulants in severely traumatized patients; and (*3*) it provides the opportunity to treat several patients per day on the same dialysis post.

Continuous hemodialysis or hemofiltration strategies allow for the gradual removal of solutes and slow correction of fluid overload. The need for continuous anticoagulation is a disadvantage, especially in traumatized patients. Loco-regional anticoagulation with sodium citrate, neutralized by administration of equivalent quantities of calcium salts, is dependent on the availability of staff familiar with this procedure.

Peritoneal dialysis is difficult to administer in patients with

abdominal trauma and often will be inefficient for the removal of potassium and other catabolic metabolites. It might offer temporary help, however, especially if during disasters mechanically driven dialytic options are not readily available.

Removal of myoglobin by plasma exchange has no demonstrated benefit and also is debatable, because the metabolic turnover of myoglobin is fast.

Rhabdomyolysis in Disaster Conditions

Epidemiology

Large numbers of patients all developing rhabdomyolysis at the same time are observed after disasters, particularly earthquakes. Starting in 1988, several earthquake disasters caused great numbers of patients with dialysis-dependent ARF. The most prominent examples include the Spitak earthquake in Armenia in 1988 (37–41) (323 patients needing dialysis), the Great Hanshin earthquake in Japan in 1995 (42–44) ($n = 156$), and most recently the Marmara earthquake in Turkey in 1999 (45,46) ($n = 462$).

It became apparent after the Spitak earthquake in Armenia that disaster response teams needed to be better equipped, with access to depots of material and logistic nephrologic support organized in advance. Relief efforts there were hampered by uncoordinated rescue teams that arrived on the scene several days after the disaster (38,39,47). To avoid problems of this kind, the International Society of Nephrology (ISN) created the Renal Disaster Relief Task Force (RDRTF) in 1995. This task force was given the job of preparing stocks of goods and lists of volunteers who could intervene immediately in the event of a large-scale disaster (48,49). The European Branch of the RDRTF recently became fully operative, and was dispatched when an earthquake with a magnitude of 7.4 struck northwest Turkey on August 17, 1999. In collaboration with the international medical relief agency Médecins sans Frontières (Doctors Without Borders), several thousand artificial kidney membranes, dialysate concentrate, dialysis catheters, and kayexalate were provided. In addition, about 30 nurses and six nephrologists from different European countries went to work to relieve the tremendous workload of their Turkish counterparts. An unprecedented number of 462 ARF patients underwent approximately 5000 dialysis sessions, with an unexpectedly low mortality rate ($<19\%$).

The number of ARF patients is influenced largely by local circumstances, such as the global mortality, the severity of the shock, the size of the disaster area, the quality of the buildings, the time needed for extrication, the triage and identification procedures, and the availability of local rescue teams and medical facilities. In Turkey, survivors were extricated up to 7 d after the event, confirming that intensive search efforts for victims should never be discontinued too soon.

Therapeutic Considerations

Timely administration of fluid in an effort to prevent ARF requires a line for infusion in a free arm or leg vein of the victim while the extrication procedure is still continuing (Table 5). In view of the substantial amount of fluid that potentially accumulates in damaged limbs, it has been proposed that during the first 24 h, up to 10 to 12 L of fluid should be administered (29).

This concept, however, was developed during a disaster of limited extent involving mainly young individuals (30), and was characterized by a rapid intervention by rescue teams, easy transportation of patients and materials, and supervision by the same aid provider of all patients from the moment of extrication until their discharge from the intensive care unit.

It may be wise to administer more limited amounts of fluid to victims of great disasters, to avoid complications resulting from a lack of close medical supervision (50). In the Marmara earthquake, we advised administering up to 6 L during the first 24 h, until the patients were admitted to the hospital where they could be better monitored. The reasons for this more cautious approach were: (*1*) the extent of the disaster, making immediate supervision difficult and the availability of appropriate sterile fluid formulations unpredictable; (*2*) the risk of impending pulmonary edema in older victims (upper limit, 90 yr); (*3*) the long periods of isolation (up to 168 h), so that prolonged anuria was a strong possibility.

Regarding dialysis modalities, we had to consider the hypercatabolic state of the victims, the frequent presence of electrolyte disturbances, the presence of polytrauma and bleeding tendency, and the specific geographic and local conditions, *i.e.*, patient overload, transport problems, and logistic difficulties. As mentioned above, conventional hemodialysis allows efficient solute removal, application without anticoagulants, and treatment of several patients per dialysis post. However, this requires the availability of undamaged dialysis facilities located at an acceptable distance from the disaster area. Fortunately, this was the case in Turkey. It might be preferable not to treat ARF patients in the disaster area. Aftershocks are frequent, and even if facilities remain operative after a first shock, they may become more severely damaged by an aftershock. Transport of ARF patients might be impossible during this later stage, further increasing mortality.

Consequently, these problems highlight the need to transport victims out of the disaster area to places where dialysis facilities have been preserved. Transport by road might be impossible, and transport by boat, helicopter, or plane may be necessary. In Turkey, relocation of the patients to Istanbul by boat along the Marmara Sea helped save many lives during the first 2 days after the earthquake, because transportation by land was almost impossible because of damaged roads and bridges. The question still unanswered is what to do if adequate dialysis facilities are not available in the area surrounding a disaster site. The best alternatives are either: (*1*) to bring into the disaster area a complete dialysis infrastructure, including water treatment, dialysis machines, and a surgical and intensive care environment; or (*2*) to transport victims to remote, fully operational dialysis facilities. Locally available infrastructure, health care possibilities, and the political situation at the moment of the disaster will be important factors in the final strategy.

Although rhabdomyolysis-related ARF carries the risk of high morbidity and mortality, rapid intervention and appropriate therapy—as was possible for victims of the Marmara earth-

quake—can improve the outcome. Given the prevalence of other earthquake-prone areas throughout the world, a lesson can be learned from the successful operation of the Renal Disaster Relief Task Force in Marmara. Advanced planning and continuous readiness of the task force hopefully will save many more lives in the future.

References

1. Zager RA: Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int* 49: 314–326, 1996
2. Lameire N, Matthys E, Vanholder R, De Keyser K, Pauwels W, Nachtergaele H, Lambrecht L, Ringoir S: Causes and prognosis of acute renal failure in elderly patients. *Nephrol Dial Transplant* 2: 316–322, 1987
3. Woodrow G, Brownjohn AM, Turney JH: The clinical and biochemical features of acute renal failure due to rhabdomyolysis. *Renal Failure* 17: 467–474, 1995
4. Gabow PA, Kaehny WD, Kelleher SP: The spectrum of rhabdomyolysis. *Medicine (Baltimore)* 61: 141–152, 1982
5. Rutecki GW, Ognibene AJ, Geib JD: Rhabdomyolysis in antiquity: From ancient descriptions to scientific explanation. *Pharos* 61: 18–22, 1998
6. Rizzi D, Basile C, Di Maggio A, Sebastio A, Introna F, Rizzi R, Scatizzi A, De Marco S, Smialek JE: Clinical spectrum of accidental hemlock poisoning: Neurotoxic manifestations, rhabdomyolysis and acute tubular necrosis. *Nephrol Dial Transplant* 6: 939–943, 1991
7. Bywaters EGL, Beall D: Crush injuries with impairment of renal function. *Br Med J* 1: 427–432, 1941
8. Bywaters EGL, Popjak G: Experimental crushing injury: Peripheral vascular collapse and other effects of muscle necrosis in the rabbit. *Surg Gynecol Obstet* 75: 612–627, 1942
9. Koffler A, Friedler RM, Massry SG: Acute renal failure due to nontraumatic rhabdomyolysis. *Ann Intern Med* 85: 23–28, 1976
10. Grossman RA, Hamilton RW, Morse BM, Penn AS, Goldberg M: Nontraumatic rhabdomyolysis and acute renal failure. *N Engl J Med* 291: 807–811, 1974
11. Adiseshiah M, Round JM, Jones DA: Reperfusion injury in skeletal muscle: A prospective study in patients with acute limb ischemia and claudication treated by revascularization. *Br J Surg* 79: 1026–1029, 1992
12. Knochel JP: Catastrophic medical events with exhaustive exercise: "White collar rhabdomyolysis." *Kidney Int* 38: 709–719, 1990
13. Schwaber MJ, Liss HP, Steiner I, Brezia M: Hazard of sauna after strenuous exercise. *Ann Intern Med* 120: 441–442, 1994
14. Barrett SA, Mourani S, Villareal CA, Gonzales JM, Zimmerman JL: Rhabdomyolysis associated with status asthmaticus. *Crit Care Med* 21: 151–153, 1993
15. Visweswaran P, Guntupalli J: Rhabdomyolysis. *Crit Care Clin* 15: 415–428, 1999
16. Slater MS, Mullins RJ: Rhabdomyolysis and myoglobinuric renal failure in trauma and surgical patients: A review. *J Am Coll Surg* 186: 693–716, 1998
17. Brumback RA, Feeback DL, Leech RW: Rhabdomyolysis following electrical injury. *Semin Neurol* 15: 329–334, 1995
18. Eiser AR, Neff MS, Slifkin RF: Acute myoglobinuric renal failure: A consequence of the neuroleptic malignant syndrome. *Arch Intern Med* 142: 601–603, 1982
19. Abraham B, Cahana A, Krivosic-Horber RM, Perel A: Malignant hyperthermia susceptibility: Anaesthetic implications and risk stratification. *Q J Med* 90: 13–18, 1997
20. Tonin P, Lewis P, Servidei S, Di Mauro S: Metabolic causes of myoglobinuria. *Ann Neurol* 27: 181–185, 1990
21. Felig P, Wahren J: Fuel homeostasis in exercise. *N Engl J Med* 293: 1078–1084, 1975
22. Poels PJE, Gabreëls FJM: Rhabdomyolysis: A review of the literature. *Clin Neurol Neurosurg* 95: 175–192, 1993
23. Brumback RA, Feeback DL, Leech RW: Rhabdomyolysis in childhood: A primer on normal muscle function and selected metabolic myopathies characterized by disordered energy production. *Pediatr Clin North Am* 39: 821–858, 1992
24. Marais GE, Larson KK: Rhabdomyolysis and acute renal failure induced by combination lovastatin and gemfibrozil therapy. *Ann Intern Med* 112: 228–230, 1990
25. Jermain DM, Crismon ML: Psychotropic drug-related rhabdomyolysis. *Ann Pharmacother* 26: 948–954, 1992
26. Grob D: Rhabdomyolysis and drug-related myopathies. *Curr Opin Rheumatol* 2: 908–915, 1990
27. Knochel JP: Hypophosphatemia and rhabdomyolysis. *Am J Med* 92: 455–457, 1992
28. Odeh M: The role of reperfusion-induced injury in the pathogenesis of the crush syndrome. *N Engl J Med* 324: 1417–1422, 1991
29. Better OS, Stein JH: Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med* 322: 825–829, 1990
30. Ron D, Taitelman U, Michaelson M, Bar-Joseph G, Bursztein S, Better OS: Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med* 144: 277–280, 1984
31. Lopez JR, Linares N, Cordovez G, Terzic A: Elevated myoplasmic calcium in exercise-induced equine rhabdomyolysis. *Pflügers Arch* 430: 293–295, 1995
32. Lopez JR, Rojas B, Gonzales MA, Terzic A: Myoplasmic Ca^{2+} concentration during exertional rhabdomyolysis. *Lancet* 345: 424–425, 1995
33. Lane JT, Boudreau RJ, Kinlaw WB: Disappearance of muscular calcium deposits during resolution of prolonged rhabdomyolysis-induced hypercalcemia. *Am J Med* 89: 523–525, 1990
34. Shieh SD, Lin YF, Lin SH, Lu KC: A prospective study of calcium metabolism in exertional heat stroke with rhabdomyolysis and acute renal failure. *Nephron* 71: 428–432, 1995
35. Oh MS: Does serum creatinine rise faster in rhabdomyolysis? *Nephron* 63: 255–257, 1993
36. Holt S, Moore K: Pathogenesis of renal failure in rhabdomyolysis: The role of myoglobin. *Exp Nephrol* 8: 72–76, 2000
37. Better OS: History of the crush syndrome: From the earthquakes of Messina, Sicily 1909 to Spitak, Armenia 1988. *Am J Nephrol* 17: 392–394, 1997
38. Collins AJ: Kidney dialysis treatment for victims of the Armenian earthquake. *N Engl J Med* 320: 1291–1292, 1989
39. Richards NT, Tattersall J, MacCann M, Samson A, Mathias T, Johnson A: Dialysis for acute renal failure due to crush injuries after the Armenian earthquake. *Br Med J* 298: 443–445, 1989
40. Noji EK: Natural disasters. *Crit Care Clin* 7: 271–292, 1991
41. Collins AJ, Burzstein S: Renal failure in disasters. *Crit Care Clin* 7: 421–435, 1991
42. Baba S, Taniguchi H, Nambu S, Tsuboi S, Ishihara K, Osato S: The great Hanshin earthquake. *Lancet* 347: 307–309, 1996
43. Kuwagata Y, Oda J, Tanaka H, Iwai A, Matsuoka T, Takaoka M,

Kishi M, Morimoto F, Ishikawa K, Mizushima Y, Nakata Y, Yamamura H, Hiraide A, Shimazu T, Yoshioka T: Analysis of 2702 traumatized patients in the 1995 Hanshin-Awaji earthquake. *J Trauma* 43: 427–432, 1997

44. Oda J, Tanaka H, Yoshioka T, Iwai A, Yamamura H, Ishikawa K, Matsuoka T, Kuwagata Y, Hiraide A, Shimazu T, Sugimoto H: Analysis of 372 patients with crush syndrome caused by the Hanshin-Awaji earthquake. *J Trauma* 42: 470–476, 1997
45. Lameire N: Preliminary report of the action in Turkey of the International Society of Nephrology Renal Disaster Relief Task Force. *Nephrol Dial Transplant* 14: 2614–2615, 1999
46. Sever MS, Erek E: Sincere thanks of Turkish nephrologists to their European friends. *Nephrol Dial Transplant* 2000, in press
47. van der Reijden HJ: Ervaringen met nierdialyse in het rampgebied van Armenië. *Ned Tijdschr Geneeskd* 133: 567–570, 1989
48. Solez K, Bihari D, Collins AJ, Eknoyan G, Eliahou H, Fedorov VD, Kjellstrand C, Lameire N, Letteri J, Nissenson AR, Noji EK, Wauters JP, Yamamoto Y: International dialysis aid in earthquakes and other disasters. *Kidney Int* 44: 479–483, 1993
49. Lameire N, Vanholder R, Clement J, Hoste E, Van Waeleghem JP, Larno L, Lambert MC: The organization of the European Renal Disaster Relief Task Force. *Renal Failure* 19: 665–671, 1997
50. Atef MR, Nadjatfi I, Boroumand B, Rastegar A: Acute renal failure in earthquake victims in Iran: Epidemiology and management. *Q J Med* 87: 35–40, 1994