Acute renal failure related to the crush syndrome: towards an era of seismo-nephrology?

Raymond Vanholder¹, Mehmet S. Sever², Ekrem Erek³ and Norbert Lameire⁴

¹Renal Division, University Hospital, Gent, Renal Disaster Relief Task Force of the International Society of Nephrology (ISN), ²Istanbul Medical Faculty, local coordinator for the Renal Disaster Relief Task Force, ³Cerrahpasha Medical Faculty, President of the Turkish Society of Nephrology and ⁴Renal Division, University Hospital, Gent, coordinator for the European Section of the Renal Disaster Relief Task Force

Introduction

The clinical crush syndrome occurs as a consequence of traumatic events, either accidents or disasters. In contrast to accidents, which affect only a limited number of individuals, disasters affect large numbers of victims simultaneously, thus provoking veritable epidemics, which often require supraregional assistance. As a result of muscular compression, myocytes are damaged, and this is followed by the release of intracellular constituents into the systemic circulation. This process is called rhabdomyolysis. One of the key compounds released is myoglobin, a 18 800 Da oxygen carrier similar to haemoglobin. In contrast to haemoglobin, however, it contains only one haeme moiety. Myoglobin is filtered by the glomeruli and reaches the tubules, where it provokes obstruction and failure of renal function [1]. Other intracellular components such as protons, phosphate, potassium, and nucleotides, i.e. precursors of uric acid, are released from the damaged muscles as well, and play an important role in crush-associated pathophysiology. Finally, volume depletion of the victim is an important determinant of renal injury [2].

Today, rhabdomyolysis is one of the leading causes of acute renal failure (ARF) [1,3]. Muscle trauma, however, does not always lead to rhabdomyolysis, not all rhabdomyolysis leads to ARF, and not all ARF related to the crush syndrome is attributable to rhabdomyolysis. Alternative causes of ARF in patients with crush injury are dehydration, sepsis, and drug nephrotoxicity. Although rhabdomyolysis is linked to trauma, most cases in peacetime are provoked by non-traumatic causes, mainly alcohol abuse, muscular compression due to coma or seizures, electrolyte disturbances (hypokalaemia, hypophosphataemia), exertion, hyper-
thermia, drug ingestion (most frequently HMGC\textsubscript{O}A reductase inhibitors and illicit psychedelic drugs), and infectious diseases [4]. Genetic defects of muscle-cell metabolism are rare and difficult to diagnose causes of repeated episodes of rhabdomyolysis [5,6].

In modern English literature, the first report of ARF related to the crush syndrome goes back to the description by Bywaters and Beall [7]. It concerned victims of the bombing of London during the Battle of Britain in the second world war. However, rhabdomyolysis had been known even in antiquity [8]. The Old Testament, for example, refers to a plague affecting the Israelites following the eating of hemlock-poisoned quail (Book of Numbers 11:31–35), a condition known to induce rhabdomyolysis [9].

Pathophysiology of the muscular lesions

The role of calcium

The pathophysiology of muscular cytolysis in the crush syndrome is based on changes in cellular metabolism. A central role is played by transcellular and intracellular calcium shifts. Under normal conditions, muscular depolarization is induced by intracellular Ca\textsuperscript{2+} released from the endoplasmic reticulum. The result is a rise of actin–myosin binding and muscular contraction. Conversely, relaxation occurs when Ca\textsuperscript{2+} is taken up again by intracellular storage organelles, a process that requires energy delivery by adenosine triphosphate (ATP) [1]. When the crush syndrome develops, excess calcium enters the muscle cell in exchange for intracellular sodium. Such large quantities of free calcium ions trigger contraction, resulting in energy depletion [6]. Furthermore, calcium activates phospholipase A\textsubscript{2}, as well as various vasoactive molecules and proteases, and induces free radical release [1]. In addition, stretching of the muscle cells increases the influx of sodium, chloride and water across the sarco-plasmic membrane, resulting in cell swelling [5]. All these events finally result in progressive muscle-cell destruction.

Intramuscular accumulation of calcium becomes irreversible when it induces massive calcification of necrotic muscles and even heterotopic ossification [10,11]. This finding explains why most patients with rhabdomyolysis develop severe hypocalcaemia during the early stages of the disease. Such hypocalcaemia may lead to cardiac arrhythmia (especially in combination with hyperkalaemia), to seizures, or to muscular contraction, thus inducing further muscular damage. Curiously enough, some patients with rhabdomyolysis do not show hypocalcaemia [4], whereas patients with non-rhabdomyolytic ARF may show a degree of hypocalcaemia similar to their matched rhabdomyolytic counterparts [4]. During later stages of the disease, the sequestered calcium is released again from the muscle, possibly [12], but not necessarily [13], associated with hyperparathyroidism and hypervitaminosis D, and resulting in overt hypercalcaemia.

Reperfusion injury

Much of the muscular damage, and especially calcium influx, takes place only after the compression of the damaged muscle has been relieved. This is analogous to reperfusion injury seen after PTA for myocardial infarction. At the moment when compression is relieved, amongst others, leukocytes migrate into the damaged tissue where they are activated and release free radicals as well as other injurious compounds. This process is further enhanced by the sudden ample availability of oxygen (reperfusion injury) [14]. Muscular hyperperfusion is provoked by inducible NO synthase which further aggravates these deleterious effects.

Compartment syndrome

Many striated muscles are contained within rigid compartments formed by fasciae, bones and other structures. If muscle cells swell, the intracompartamental pressure rises and this causes additional damage and necrosis. Since such compartments are non-communicating closed systems, the only way to decrease the pressure is to surgically decompress the fascial system by fasciotomy or by mannitol administration [15]. Not all authors are overly enthusiastic about fasciotomies, as they are a potential source of later infection [15]. On the other hand, prolonged pressure may provoke irreversible damage to peripheral nerves, with paralysis and drop foot as consequences. It is generally accepted that compartment pressures above 30 mmHg produce clinically significant muscular ischaemia. In hypotensive patients, even lower compartment pressures will cause perfusion problems.

Pathophysiology of ARF in rhabdomyolysis

At the kidney level, the main pathophysiological events in the genesis of myoglobinuric ARF are renal vasocostriction, intraluminal cast formation, and direct haeme-protein-induced cytotoxicity [1]. Myoglobin is easily filtered through the glomerular basement membrane and passes into the tubules. When water is progressively reabsorbed from tubular fluid, the concentration of myoglobin rises until it precipitates, causing obstructive cast formation. Likewise, the high rate of uric acid generation and excretion may additionally contribute to tubular obstruction. These processes leading to obstruction are aggravated by renal vasocostriction and a decreased glomerular perfusion pressure. They result from intravascular hypovolaemia caused by uptake of water by the damaged muscles. It is not uncommon for more than 10 litres of fluid to accumulate in the damaged limbs. The fall in glomerular filtration decreases urinary flow and enhances tubular water reabsorption [1]. Another factor in the precipitation of myoglobin and uric acid is a low pH.
in tubular urine. When pH decreases, the solubility of myoglobin is progressively lost. Solubility is mediated largely by Tamm–Horsfall protein, a charged pH protein. The intratubular disintegration of the iron-carrying myoglobin leads to the release of iron, which catalyses free radical production. These free radicals further potentiate ischaemic renal damage. In addition, gastrointestinal ischaemia favours endotoxin absorption and release of cytokines, which further enhances the inflammatory reaction and haemodynamic instability.

These pathophysiological mechanisms have important therapeutic implications. Intravascular dehydration and myoglobin precipitation in the tubules must be prevented at all costs; this is the rationale behind the strategy of early and aggressive administration of fluid and alkalization of urine.

**Diagnosis**

By definition, myoglobinuria is the central element in the development of rhabdomyolysis-induced ARF. Although myoglobinuria does not exist without rhabdomyolysis, rhabdomyolysis itself does not necessarily result in detectable myoglobinuria. For diagnostic purposes, the measurement of myoglobin in plasma or urine is unreliable, because myoglobin is metabolized in the liver quickly and in an unpredictable fashion. Myoglobin may already have disappeared from the blood when the patient is admitted, but if it is still present, it will not cause a red discoloration of the plasma, in contrast to haemoglobin. Myoglobin in the urine, on the other hand, provokes a typical red-brown discoloration (Port wine-like). The benzidine urinary dipstick for haeme detects both myoglobinuria and haemoglobinuria as well as erythrocyturia. It does not distinguish between these three conditions.

The enzyme creatine kinase (CK) is ubiquitously present in striated muscle. When muscle cells disintegrate, CK is released into the blood stream. Several subtypes of CK exist, some of them being contained in striated muscles (CKMM), others in cardiac muscle (CKMB). During rhabdomyolysis, large quantities of CKMM are released into the blood stream. Peak concentrations of 100,000 IU/ml or more are not unusual. Since the degradation of CKMM is slow and the enzyme is not removed by the kidneys or by dialysis, the plasma concentration of CK remains elevated much longer and in a more consistent fashion than that of myoglobin. Consequently, CK is a more reliable marker to assess the presence and intensity of muscle damage than is myoglobin.

**Prevention and treatment**

The prime therapeutic principle is the interruption of the patho-physiologic cascade leading to ARF. The damaged muscles attract substantial amounts of plasma water and sodium. The ensuing hypovolaemia can be prevented by aggressive administration of intravenous fluids [15]. To obtain normal values of plasma volume, administration of up to 10 litres or more of fluid per day may be required. In traumatized subjects at risk of rhabdomyolysis, it is important to start fluid administration before the victim is extracted from under the rubble [2].

The ideal fluid regimen consists of half isotonic saline (0.45% or 77 mmol/l of sodium) to which 100 mmol/l of sodium bicarbonate is added. Alkali prevents acidification of the urine, which promotes tubular precipitation of myoglobin. Alkali also reduces the risk of hyperkalaemia, caused by leakage of potassium from damaged muscle cells.

This fluid combination can be completed by 10 ml/h of mannitol 15%, if the patient continues to have a diuresis. Mannitol is a renal vasodilator, it increases glomerular pressure, attracts fluid from the muscular and interstitial compartments, increases urine flow, prevents tubular obstruction by myoglobin deposits, and acts as a free radical scavenger. Mannitol should, however, be withheld if the patient develops oligoanuria.

Once renal failure is established, the only reliable therapeutic modalities are removal strategies (dialysis and/or adsorbants). Indications for dialysis are not only high urea concentrations, but also hyperkalaemia and acidosis. Fluid overload is only rarely an indication to start dialysis, because large amounts of fluid are sequestered by the damaged muscle. Conventional intermittent haemodialysis has several advantages in this condition of severe hypercatabolism because of: (i) the possibility of efficiently removing ureaemic solutes, including potassium, phosphate and protons; (ii) the possibility of dialysing traumatized patients without need for anticoagulants; (iii) the possibility of treating several patients per day at the same dialysis post.

Continuous dialysis strategies offer the opportunity of gradually removing solutes together with fluid. One of the major disadvantages is their need for continuous anticoagulation, which is problematic in traumatized patients, especially if they have undergone fasciotomy. Peritoneal dialysis is difficult to use in patients with abdominal trauma, and might not be sufficiently efficient for the required high rates of removal of potassium and other catabolic metabolites. It might offer temporary help, however, particularly in disaster areas where mechanically driven dialysis possibilities are not readily available.

**Towards the era of seismo-nephrology**

The most impressive numbers of simultaneously developing cases of rhabdomyolysis are observed during disasters. Amongst them, earthquakes have recently attracted most attention. From 1988 on, several earthquake disasters caused a substantial number of dialysis dependent cases of ARF. The most prominent examples include the Spitak earthquake in Armenia in
1988 [16-20] (323 patients needing dialysis), the Great Hanshin earthquake in Japan in 1995 [21-23] (n=156) and most recently the Marmara earthquake in Turkey in 1999 [24,25] (n=462).

Probably because of the early action taken by nephrologists, the availability of precise action plans, and the accessibility of listed volunteers and stored goods, a surprisingly low mortality of 20% of the dialysed ARF patients could be achieved in the Marmara earthquake. We can only wish, but unfortunately cannot be certain, that disasters of a similar extent will occur no more in the 21st century. If they do occur, however, adaptation of the action plans will hopefully help to further reduce patient mortality.

It has been argued (i) that ARF affects only a limited proportion of all earthquake victims, (ii) that dialysis is an expensive and highly technological therapeutic option, and (iii) that more urgent needs (e.g. housing, primary health care, hygienic measures) affecting larger proportions of the victimized population are more important. However, severe crush syndrome victims are extricated with immense efforts from under the rubble. It would be deplorable if, having been extricated at such expense, the unhappy victims were not offered all therapeutic possibilities to prevent or treat ARF.

It has become apparent after the Spitak earthquake in Armenia, in December 1988, how important it is to have structured advance material and logistic nephrological support. One of the problems then were the uncoordinated relief efforts by rescue teams that arrived on the scene only several days after the disaster [17,18,26]. To avoid problems of this kind, the International Society of Nephrology (ISN) has installed the Renal Disaster Relief Task Force (RDRTF). Three different sections are responsible for the European, American and Pacific area. These task forces should prepare stocks of goods and lists of volunteers who could intervene immediately in case of a large-scale disaster [27,28]. The European Branch of the RDRTF recently became fully operative, when an earthquake with an intensity of 7.4 on the Richter scale struck North-West Turkey on 17August 1999. Support consisted of several thousands of artificial kidneys, dialysate concentrates, dialysis catheters, and keyexalate. In addition, close to 30 nurses and six nephrologists from different European countries went to work on the spot in Turkey, in order to relieve the tremendous workload of their Turkish colleagues. An unprecedented number of 462 ARF patients underwent close to 5000 dialysis sessions, with an unexpectedly low mortality rate (<20%). The first help was provided only a day after the disaster.

During the action in Turkey, the team made a substantial effort to administer large quantities of saline in time. Ideally, this was started before the extrication of the victims from under the rubble, as originally suggested by Better and Stein [15]. Efforts were made to instruct primary care workers about the importance of this measure. Pamphlets in Turkish were distributed in the disaster area at locations where primary help and triage took place before patients were transported further.

Regarding dialysis modalities, a number of factors had to be taken into consideration such as the hypercatabolic state, the electrolyte disturbances, the presence of polytrauma and bleeding tendency, the specific geographic and local conditions creating patient overload, problems of patient transport to dialysis facilities, and logistic difficulties. As mentioned above, haemodialysis allows efficient solute removal, it can be performed even without anticoagulants, and it allows treatment of several patients per post. This necessitates, however, the presence of dialysis equipment with adequate water-treatment facilities, and experienced nurses, nephrologists, and technicians within a reasonable distance of the disaster area. This was fortunately the case in North-West Turkey. In addition, the Turkish staff made heroic efforts to save lives and relieve suffering.

As a result of the above considerations, it might be preferable not to treat ARF patients in the disaster area, because this will undoubtedly lead to mortality rates that are higher than when patients are treated in back-up hospitals within the surrounding area [22]. Even if dialysis facilities are still operational after a first earthquake, there is a constant risk that they may be destroyed if an aftershock occurs. Transport of ARF patients might be impossible during this later stage, thus further increasing mortality substantially. Consequently, there remains a need for immediate transport of victims with ARF or with impending ARF out of the disaster area to areas where dialysis facilities have remained intact. This transport might be impossible by road, and transport by boat, helicopter or plane may be necessary.

The unsettled question that remains is what to do if, in the area surrounding the disaster region, there are no adequate and sufficient dialysis facilities. The alternatives are: (i) to bring into the disaster area a complete dialysis infrastructure, including water treatment, dialysis machines, and surgical and intensive care environment, with temporary non-power driven modalities such as PD or CAVH as an alternative to bridge the gap, or (ii) to transport of victims to remote, fully operational dialysis facilities. The latter solution is preferable except in cases of disasters creating huge numbers of victims. In these cases the local and international nephrological communities might be confronted with an almost impossible task.

It is difficult to tell precisely how many lives have been saved by the offered help. We are certain, however, that the moral as well as the financial and logistic support offered by the international community has helped Turkish nephrologists and nurses to cope with the immense problems with which they had been confronted [24,25]. The experience gained in the aftermath of the Marmara earthquake will help to improve our practical approach in case of future devastating earthquakes.
24. Sever MS, Erek E. Sincere thanks of Turkish nephrologists to their European friends. *Nephrol Dial Transplant* (in press)