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The Mechanism of Muscle Injury in the Crush Syndrome: Ischemic versus Pressure-Stretch Myopathy[1]

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Abstract. Crush injuries are ubiquitous, common sequelae in victims of seismic, industrial and military catastrophes, and were considered to be mainly due to ischemia of the affected limbs. Our clinical experience suggests that early in the crush syndrome, interference with the circulation may occur but is rare. The predominant earliest lesion in the crush syndrome is postulated to be pressure-stretch myopathy, rather than ischemic myopathy. It is proposed that at the membrane level, stretch increases sarcoplasmic influx of Na, Cl, H_2O and Ca down their electrochemical gradient. Energy-requiring cationic extrusion pumps work at maximal capacity, but are unable to cope with the increased load. This results in cell swelling and increase in cytosolic and mitochondrial calcium with activation of autolytic destructive processes and interference with cellular respiration. Extensive muscle swelling may cause late muscle tamponade and myoneural ischemic damage (compartmental syndrome). Thus, whereas prevalent theory suggests that the sarcolemmal cationic pump activity is attenuated in the crush syndrome due to early ischemia, we propose that the cationic extrusion pump is maximally activated as in the amphotericin B model. Because the cationic pump is maximally activated in the stretched muscle and in cells exposed to amphotericin, these models rapidly deplete their scarce ATP stores and are susceptible to hypoxia in the face of initially normal circulation.

The proximity of our hospital to the Lebanese theater of war and the extensive two-way use of the helicopter enabled us in the last 15 years to examine and manage many victims of the crush syndrome (CS) very early, i.e. during or immediately following extrication from under the debris [1]. Signs elicited during careful physical examination of crushed limbs led us to reassess the conventionally held views on the pathogenesis of rhabdomyolysis in this type of trauma. The purpose of this communication is to focus on the pathogenesis of the myopathy associated with CS at the membrane and cellular level.

During the darkest days of the Battle of Britain and the Blitz of London almost 50 years ago, Bywaters and

Beall [2], Bywaters and Popjak [3] and Bywaters and Stead [4] presented the definitive, classic description of CS. Although their clinical observations and most of their guidelines for therapy have withstood the test of time, the cellular mechanism of CS remains controversial. In the above-cited publications [2–4], the authors stressed the importance of ischemic myopathy in CS. They based this impression on the absence of pedal pulses and ischemic distal necrosis of the involved extremities in some of their patients with CS. Others confirmed the ischemic component of CS. Among them is Knochel [5], who described the 'second wave phenomenon' in limbs with extensive rhabdomyolysis. Approximately 36 h after the initial lesion, during an apparent clinical and biochemical recovery, he observed the secondary development of muscle tamponade leading to

occlusion of the circulation to the distal part of the limbs, fresh muscle necrosis and a late increase in blood creatine phosphokinase (CPK) levels [5]. Knochel suggested that in exertional rhabdomyolysis there was ischemic depletion of cellular stores of ATP [6]. According to this scheme, ATP depletion would exhaust the energy source for the sodium extrusion pump and thus attenuate its function. Such suppression of the sodium pump, in turn, would have several adverse effects on membrane integrity and cellular metabolism. Among these are partial obliteration of sarcoplasmic negative-potential difference, increase in cell sodium chloride, water and calcium, decrease in cell potassium and, ultimately, cell swelling and death [6]. Indeed, an increase in injured-muscle sodium, water and calcium content was reported by Meroney et al. [7] in dogs with traumatic rhabdomyolysis as well as in man with 'nontraumatic' rhabdomyolysis [8–10].

Akmal et al. [10] demonstrated in man, in vivo, the striking, massive nature of the calcium influx into traumatized muscles. The rapidity and magnitude of calcium uptake by the injured muscle in man [10] and the dog [7] raise the possibility that injured muscles are susceptible to increased leakiness of the sarcolemmal membrane to solutes and water. Interestingly, Knochel tacitly left open the possibility that increased permeability of the cell membrane contributed to cell swelling in rhabdomyolysis. He based his provocative findings and conclusions mainly on subjects with exertional rhabdomyolysis and on dogs with severe, experimental potassium depletion and hypokalemia [6]. Hypokalemia was critical to the development of exertional rhabdomyolysis because Knochel showed that hypokalemia caused vasoconstriction and interfered with muscle oxygenation. Knochel's conclusions, therefore, may not be applicable to traumatic rhabdomyolysis or CS, which almost invariably lead to hyperkalemia [1, 11]. It is quite possible that exertional rhabdomyolysis and hypokalemic rhabdomyolysis are, pathophysiologically, a 'mild form of CS', and therefore may be quantitatively and perhaps even qualitatively different from full-blown massive mechanical crush injury.

Examining the injured limbs of victims of CS, one must come to the conclusion that in the great majority of patients, the perfusion of the distal limbs is intact. This is based on the presence of normal distal pedal pulses as well as normal circulation of the skin in the face of extensive crush lesion and muscle swelling. Normal distal perfusion was seen even in persons who were trapped more than 28 h under fallen masonry and suffered from extensive rhabdomyolysis [1, 11]. Moreover, total warm ischemia of more than 4 h in man should have invariably led to massive necrosis of the extremities. Hence, physical examination and the constraints of warm ischemic time in trapped victims raise serious doubt that ischemic myopathy is a predominant common cause for their CS. Others reached similar conclusions [12]. In the dog model of compartment syndrome, upon increasing interstitial pressure in the anterior tibial compartment to 100 mm Hg, we regularly witnessed intact distal circulation as proven by the presence of normal pedal pulses and angiographically patent vessels to the distal limb [13].

If our conclusion that in the majority of patients with massive CS *early* ischemia is not etiologically of major importance is correct, what then is the cause of the myopathy and striking swelling of the injured muscle?

Skeletal muscle appears to be exquisitely sensitive to pressure. One estimate puts it at 100–1,000 times more sensitive to acute pressure than the skin [11]. In our canine compartment syndrome model we found that an increase of interstitial pressure within the anterior tibial compartment of 100 mm Hg for 60 min will cause extreme rhabdomyolysis and advanced neuronal damage. In marked contrast, total ischemia of the dog limb of 60 min will not cause any damage, and this is well borne out by the common orthopedic practice in man of operating in an intentionally ischemic field for up to 2.5 h during normothermia without causing ischemic damage.

Extreme external pressure on the muscles in trapped persons, following the collapse of buildings during earthquakes, or the mere pressure of the torso on a wedged limb will cause increased intramuscular pressure of up to 240 mm Hg [14] (normal: < 4.0 mm Hg). Such pressure, by itself, independently of ischemia, may damage the muscle (baromyopathy). The mechanism of baromyopathy appears to be increased sarcolemmal leakiness to solutes and water, due to stretch forces. Indeed, provocative studies on the effect of mechanical stretch on membrane permeability in cultured skeletal muscle and in nerve cells showed that stretch will activate cation entry into the cells [15, 16]. Stretch-activated cation entry into cells may overwhelm the finite, maximal capacity of the cationic extrusion pumps (mainly Ca-ATPase and Na-K-ATPase). Theoretical considerations support such a contention. Whereas the opening of a single-membrane cationic channel under the influence of stretch may admit into the cell 10^8 cations per second, the capacity of an extrusion pump is only 10^2 ions per second [17]. In other words, relative to the slow cationic pump turnover,

cationic channels have a several orders of magnitude larger turnover (extremely short cationic transit time). Thus, in unit time, the cationic influx through a single cationic channel will engage the activity of 10^6 Na-K-ATPase pumps [17]. Under basal conditions, cationic leakage down the electrochemical gradient into the cell is matched by energy-consuming cationic pump extrusion activity. Mechanical stretch, by increasing the cationic influx, undermines this balance [17]. The end result of stretch, therefore, would be flooding of the cytosol (sarcoplasm) with Na, Ca, Cl and water, and cell swelling. The inappropriate increase in cytosolic calcium concentration creates metabolic havoc ('cytosolic Ca becomes an ionic assassin' [18]) by precipitation with the high cytosolic and mitochondrial contents of phosphate, and by activation of neutral phosphatases and other autolytic enzymes. Ultimately, mitochondrial calcium apatite deposition will interfere with mitochondrial respiration and deplete its scarce stores of energy (ATP).

Thus, a late effect of stretch is suppression of cellular respiration and cell swelling (hypoxia rather than ischemia). In muscle groups confined to noncompliant fibrous sheaths as in the forearm or the calf, all swelling will lead to tamponade and ischemic myoneural damage (the compartment syndrome). In other words, pressure myopathy causes ischemic myopathy which, in its turn, increases muscle interstitial pressure (destructive 'positive feedback').

Seen from this angle, comatose addicts who, during immobilization compress their limbs, suffer initially, predominantly from pressure myopathy, perhaps aggravated by toxic myopathy due to substances like alcohol [19], cocaine [20], heroin or amphetamines [21] or by physical factors such as hyperthermia or convulsions caused by the latter [21]. In view of the mechanical pressure and increased muscle stretch associated with coma and wedging of limbs [14–16], the term *'non'*-traumatic rhabdomyolysis [8, 9] should be modified.

Modern sophisticated monitoring of in vivo tissue oxygen tension, intramuscular interstitial pressure and regional muscle blood flow by Doppler techniques will help to distinguish between the pressure phase and the ischemic phase of myopathy, and perhaps even delineate and define the transition of the former into the latter. It is quite possible that in analogy with type B lactic acidosis, in which the circulation and cellular O_2 supply are intact, in CS we will find myopathy due to interference with cellular respiration, yet with initially normal circulation and external O_2 supply.

The clinical implications of shifting the emphasis in early crush injury from ischemia to pressure myopathy are not clear at present and would not change present-day-recommendations for rescue and salvage operations [11]. On the experimental level, it remains to be seen whether, in early muscle injury, a calcium-blocking agent could reduce membrane leakiness to calcium.

We conclude that in many patients with 'nontraumatic rhabdomyolysis', and perhaps in all victims of CS, there is an early phase of exertion of blunt, sustained pressure on the skeletal muscles that may reach twice the normal arterial blood pressure [14]. Such pressure will cause stretching of the sarcolemmal membrane and increase membrane leakiness to solutes and water [15, 16]. Sodium extrusion pumps are postulated to work at maximum capacity to cope with the increased penetration of solutes down their electrochemical gradient into the sarcoplasm.

When the cellular calcium buffering capacity is undermined by mitochondrial calcium deposition, cellular respiration will be further compromised and cytosolic calcium will rise. Such an increase in cytosolic calcium will activate a series of cytolytic enzymes, among them phospholipases, proteases, nucleases, glycogen phosphorylases and many others. The end result will be a further reduction of the sarcolemmal membrane integrity and the depletion of ATP stores in a cell whose extrusion pump activity is already overtaxed. According to this scheme, extreme stretch damage to the membrane will cause a cationic-transport-dependent damage, superficially, reminiscent, of the effect of polyene antibiotics (amphotericin B) which increases membrane leakiness [22]. Such damage taxes ionic extrusion capacity and predisposes the cells to ATP depletion and anoxic injury [22].

Once the ionic extrusion capacity of the compressed muscle is overwhelmed, the typical cell swelling of the crushed muscle will occur. Since muscles are the bulkiest organ in the body, muscle swelling may sequester the entire extracellular fluid [11, 21] within hours to days. This is the main cause of the profound shock of rhabdomyolysis of any kind. Unless treated promptly, this 'third-spacing' shock will, within hours, become irreversible. At the muscle level, diminished arteriolar perfusion pressure, on the background of increased arteriolar resistance due to an increase in muscular interstitial pressure, will lead to muscle tamponade and ischemic myoneural damage (compartmental syndrome). Thus, the earliest phase of the potentially fatal CS is due to a stretch-dependent cellular transport disorder of the affected muscles.

Acknowledgments

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