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REVIEW

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Pathogenesis and treatment of renal dysfunction in rhabdomyolysis

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Abstract Rhabdomyolysis is a major cause of acute renal failure, and recent experimental data have provided a better understanding of the pathophysiology of the renal dysfunction. Renal failure is due to renal vasoconstriction, tubular damage caused by oxidant injury, and possibly tubular obstruction. Recent studies have provided greater insight into the rationale behind current therapy and potential treatment strategies. This review thus aims to summarise current understanding of the causes, pathogenesis and treatment of renal failure caused by rhabdomyolysis.

Key words Rhabdomyolysis · Myoglobin · Crush syndrome · Lipid peroxidation · Renal failure

Introduction

Rhabdomyolysis, or myocyte necrosis, results from a rapid rise in intracytoplasmic calcium concentrations. Cell damage or death causes the release of myocyte intracellular contents into the circulation, causing distal organ dysfunction and profound metabolic upset. The association of brown granular casts (Fig. 1) and acute renal failure (ARF) after crush injury was noted by Bywaters and Beall [1] during the wartime bombing of London. During peacetime, rhabdomyolysis is responsible for 5–7% of all causes of acute renal failure in the USA. This figure rises dramatically during wars or major disasters; for example, nearly 50% of survivors pulled from collapsed buildings develop rhabdomyolysis [2]. In the Kobe (Japan) earthquake in 1995, ~5% of the affected population suffered a crush injury [3], while ~400 people in the Armenian earthquake of 1988 required dialysis [4].

Nearly one in 1000 patients admitted to hospital have an elevated creatine kinase (CK) level; of those with CK > 5000, more than 50% develop acute renal failure [5]. The causes of rhabdomyolysis are summarised in Table 1. In one study alcohol was the most commonly associated aetiological factor [6], causing collapse, coma and disruption of muscle metabolism.

Clinical features in man

Electrolyte complications

Myocyte injury is accompanied by influx of sodium and calcium into the cytoplasm. Efflux of other ions into the extracellular fluid can result in hyperkalaemia, hyperuricaemia, hyperphosphataemia, hypocalcaemia and an early fall in plasma pH, due partly to the formation of lactate [7]. In addition to being directly cardiotoxic, the hypocalcaemia and hyperkalaemia can impair cardiovascular function. A late feature of rhabdomyolysis is the development of hypercalcaemia, reflecting the egress of calcium out of damaged and recovering myocytes, a reactive increase in parathyroid hormone levels, and restoration of 1,25-dihydroxycholecalciferol synthesis by tubules [8]. Heterotopic calcification may occur in the damaged muscle [9], and

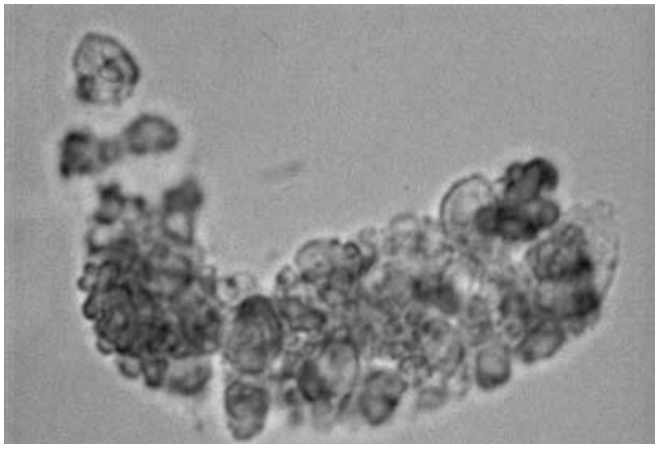

Fig. 1 Granular cast seen in the urine after rhabdomyolysis under light microscopy. (Courtesy of Dr P. Sweny, Royal Free Hospital)

this is exacerbated by exogenous calcium administered to correct early hypocalcaemia. This can be visualised clinically when technetium (^{99}Tc) MDP bone scanning is performed, showing uptake in affected muscle (Fig. 2).

Table 1 Causes of rhabdomyolysis

Category	Specific aetiological factors
Physical	*Trauma*, hyperthermia, hypothermia, exercise, electrical injury, seizures, delirium tremens
Toxins and drugs	*Alcohol*, amphetamines, aspirin (O/D), barium, barbiturates, caffeine, carbon monoxide, Ecstasy, ethylene glycol, HMGCoA reductase inhibitors, LSD, malignant hyperpyrexia, neuroleptic malignant syndrome, opiates, toluene, snake/insect bites, buffalo and turbot fish, vasopressin
Muscle ischaemia	Coma, major vessel compromise, sickle cell disease, surgery, vasoconstrictors, CO_2 angiography, thrombosis, tetanus
Infection	Virtually any viral or bacterial infection, e.g. influenza, HIV, EBV, *Legionella*, tetanus, malaria, *Bacillus cereus*, polio; toxic shock syndrome
Metabolic	Hypokalaemia, hypocalcaemia, hypophosphataemia, hyper/hyponatraemia, diabetic ketoacidosis, diabetic hyperosmolar coma, water intoxication, myxoedema
Inherited	Deficiency of carnitine palmitoyl transferase II, phosphofructokinase, myophosphorylase (McArdle's), myoadenylate deaminase, cytochrome oxidase, succinate dehydrogenase, coenzyme Q10 deficiency, King-Denborough syndrome, Wilson's disease
Immune	Polymyositis, dermatomyositis

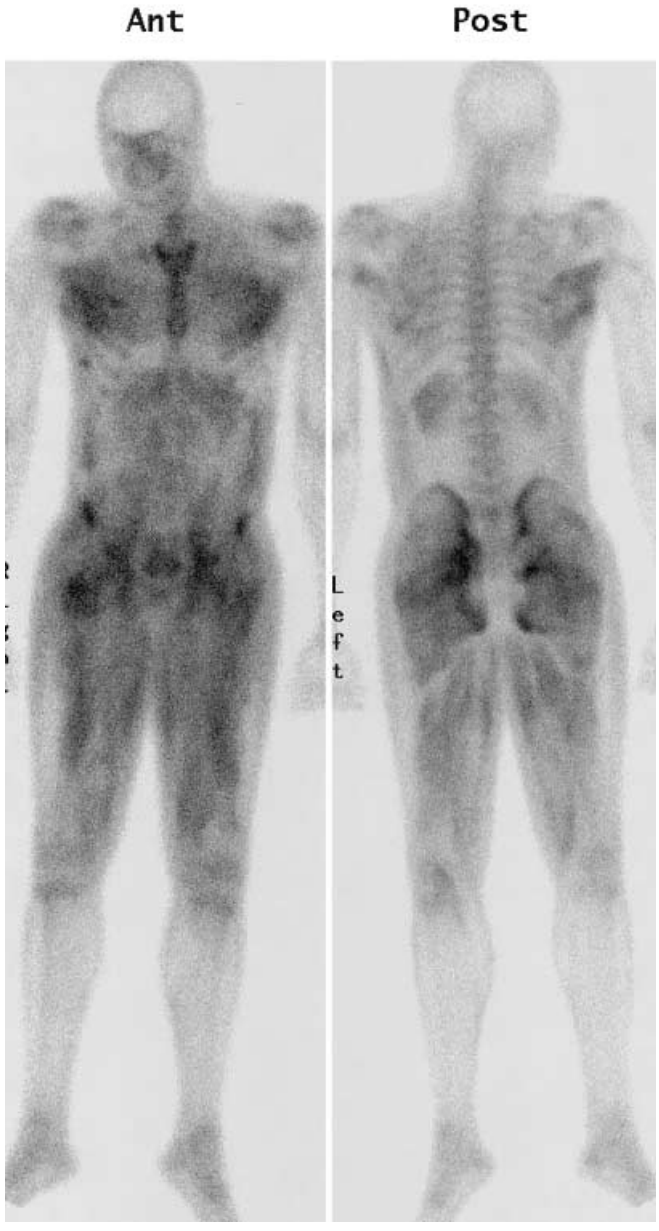

Fig. 2 ^{99}Tc Bone scan in a patient with rhabdomyolysis showing uptake into rhabdomyolysed muscle, especially in buttock and thigh *(arrow)*. (Courtesy of Dr A. Hilson, Dept. of Nuclear Medicine, Royal Free Hospital)

Diagnostic features

Release of large quantities of the muscle enzymes CK, aspartate transaminase (AST) and lactate dehydrogenase (LDH) into plasma are pathognomonic of this condition. The degree of elevation of CK is proportional to the muscle injury [10].

It has been suggested that a high creatinine-to-urea ratio assists diagnosis; however, this observation may

merely reflect the fact that young muscular males are over-represented in the population of patients with rhabdomyolysis [11]. Myoglobinuria can be inferred by a positive result on an orthotoluidine dipstick test (test for haem), usually with a mild degree of proteinuria and the absence of red blood cells on microscopy. However, up to 18% of patients are negative to such tests [12]. It should be noted that haematuria can be present concurrent with myoglobinuria, especially in the setting of trauma. Laboratory measurement of myoglobin is based on latex-enhanced immunoturbidimetric or agglutination assays. More recently, myosin heavy chain has been shown to be a sensitive marker of previous rhabdomyolysis and is detectable in plasma up to 12 days post insult [13].

Fluid balance

Following injury, there is movement of fluid from intravascular compartments into the damaged muscle and interstitium, causing profound intravascular volume depletion that may exceed 15 l [14].

Assessing severity

The severity of the ARF appears to be roughly proportional to the amount of crushed muscle. Thus, quantitative assessment of circulating or urinary myoglobin has been advocated as a useful predictor of ARF. In one study of patients with rhabdomyolysis, renal impairment was predicted by urinary myoglobin concentrations above 20 mg/l, while patients with concentrations below 18 mg/l did not develop renal failure [15]. A scoring system has been devised to identify patients with a ≥50% risk of ARF [16]; this is based upon a number of clinical measurements essentially reflecting the amount of muscle damage and complications.

Mechanism of myocyte death

An increase in cytoplasmic calcium concentrations is central to the mechanism of muscle destruction [17]. Microelectrode studies show that intracellular calcium rises to 1.27 μmol/l after induction of rhabdomyolysis, compared with ~0.12 μmol/l in normal muscle [18]. Although myocyte death occurs at the time of crush injury, the re-establishment of blood flow causes further cell death due to reperfusion injury [19]. Reperfusion also increases neutrophil recruitment and activation, with further exacerbation of oxidant injury [20].

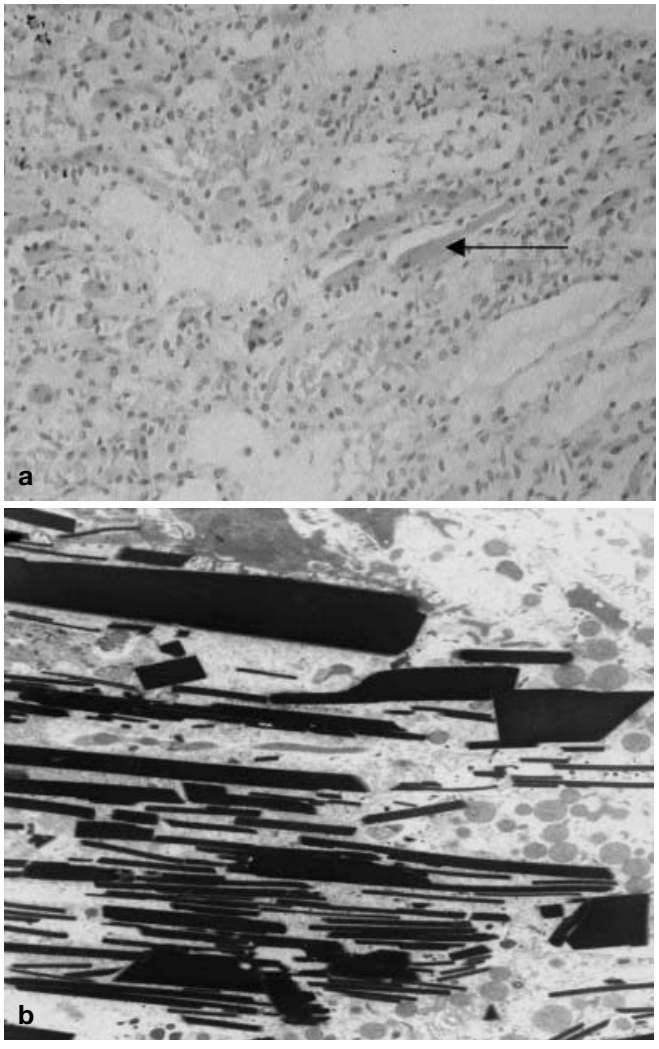

Fig. 3 **a** Low-power H&E section of rhabdomyolysed rat kidney, clearly showing numerous tubular casts as amorphous material in the tubules (*arrow*, cross-cut tubule with cast). **b** Electron micrograph of a myoglobin cast, showing the crystal-like structure of myoglobin-Tamm-Horsfall protein aggregates precipitating in the tubules

Mechanisms of acute renal failure

There are three main pathways through which rhabdomyolysis leads to the development of renal failure: tubular obstruction, tubular damage by oxidant injury, and vasoconstriction.

Tubular obstruction

Precipitation of myoglobin occurs within the tubules (Fig. 3a,b), seen in the urine as dark brown pigment casts. Myoglobin is concentrated in the tubules and pre-

cipitates readily when it interacts with Tamm-Horsfall protein (THP). This binding is enhanced under acidic conditions, and a reduction in cast formation is said to occur following alkalinisation of the urine in vivo [21]. The increased urinary urate may also precipitate, contributing to tubular obstruction. Traditionally, myoglobin was seen as an inert participant causing tubular obstruction and tubular dilatation [22]. However, kidney micropuncture experiments have shown that intratubular pressures are low, and that perfusion of the segment with buffer at low or normal pressures easily removes the casts [23]. This suggests that casts are formed as a consequence of poor washout, rather than of obstruction per se.

Tubular necrosis and the role of lipid peroxidation

Haem protein injury can affect all parts of the nephron, but especially the proximal tubule. There is now good evidence of free radical-mediated injury, as endogenous radical scavenging compounds are consumed while antioxidant administration can improve renal function [24, 25, 26]. Haem-loaded proximal tubular cells show progressive cytotoxicity, with accumulation of malondialdehyde indicative of oxidant injury [27]. Fenton chemistry, i.e. generation of hydroxyl radicals by Fe^{2+}, has been suggested as the mechanism for this oxidant injury. The inference drawn from invoking the Fenton reaction is that there is increased generation of hydroxyl ions by free iron:

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH^{\cdot}$$

$$\text{Lipid} \longrightarrow \text{Lipid peroxidation}$$

The Fenton reaction generates hydroxyl radicals ($OH^{\cdot}$), which initiate lipid peroxidation by hydrogen abstraction from unsaturated lipids. Evidence that this reaction occurs is largely indirect. An alternative mechanism invokes the ability of myoglobin itself to catalyse lipid peroxidation, which can be initiated directly by endogenous lipid peroxides or by hydrogen peroxide [28]. This mechanism involves redox cycling of the haem iron between the ferric (Fe^{3+}) and ferryl (Fe^{4+}) states. Although iron haem centres in muscle are usually in the ferrous (Fe^{2+}) state, Fe^{2+} is readily oxidised to the ferric (Fe^{3+}) state on release:

$$Mb[Fe^{3+}] + LOOH \rightarrow Mb[(Fe^{4+} = O_2^{-})] + LO^{\cdot} + H^+$$

Ferric iron centres within myoglobin react with lipid hydroperoxides (LOOH) to form lipid peroxide radicals ($LO^{\cdot}$) via formation of the ferryl (Fe^{4+}) species

Desferrioxamine (DFO), an iron chelator, protects animal models of rhabdomyolysis from renal dysfunction [29]. This led to the suggestion that free iron was important; however, it is now known that DFO also protects the redox state of haem proteins and prevents the redox cycling of myoglobin, and thus lipid peroxidation [30].

An alternative and more plausible hypothesis has emerged recently, namely that the haem group of myoglobin is the direct cause of lipid peroxidation [31]. Haem oxygenase (HO) catalyses the breakdown of haem into biliverdin, iron and carbon monoxide and is present in three isoforms. HO-2 and HO-3 are constitutively expressed at low levels in many tissues, while HO-1 is a stress protein induced in response to oxidative stress. This enzyme is rapidly up-regulated in myoglobinuric ARF [32]. It has been proposed that HO is central to the pathogenesis of haem protein-induced tubular cell death by liberating free iron. Thus, inhibition of HO should protect the kidney against myoglobin toxicity. In vitro, tin protoporphyrin, a competitive inhibitor of haem oxygenase, does indeed protect proximal tubular cells isolated from glycerol-treated animals from lipid peroxidation and cell death [33]. However, these experiments do not adequately mimic the relatively hypoxic and acidic milieu of tubular cells in vivo. Thus, when haem oxygenase inhibitors are used in vivo the reverse appears to occur, with exacerbation of tubular injury. This suggests a protective effect of haem oxygenase and argues against a role for free iron. Furthermore, induction of haem oxygenase with a priming dose of myoglobin protects renal function during subsequent rhabdomyolysis [32]. Likewise, the observation that the HO-1 gene is up-regulated exclusively in distal parts of the nephron while the proximal tubule is the primary site of injury also suggests a renoprotective effect [34]. Finally, more recent evidence has shown that rhabdomyolysis in HO knockout mice causes lethal renal impairment at doses that cause only moderate renal impairment in normal animals [35].

Renal vasoconstriction

Following induction of experimental rhabdomyolysis there is a rapid reduction in renal blood flow. The circulating blood volume decreases following movement of fluid into the damaged muscle from the extracellular compartment. These volumes may be large [36], reducing the effective blood volume and activating homeostatic mechanisms to maintain the circulating volume. Thus, there is activation of the sympathetic nervous system and the renin-angiotensin system.

In addition, a number of vasoactive mediators have been suggested to be important in reducing renal blood flow. Nitric oxide (NO) is intimately involved in maintaining renal blood flow, especially to the renal medulla [37]. NO donors preserve renal function during haem

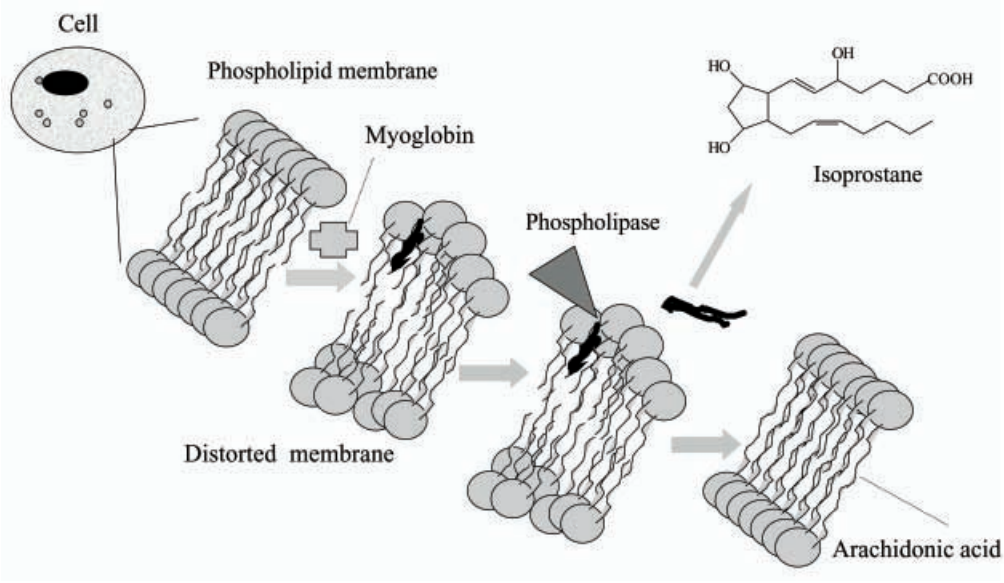

Fig. 4 Synthesis and cleavage of isoprostanes in plasma membranes. Free radical attack on arachidonic acid forms an isoprostane esterified to membrane phospholipid, and this perturbs the membrane structure. Phospholipase cleavage restores membrane integrity and releases free isoprostane

protein injury, while NO synthase inhibitors exacerbate injury [38]. This may be due to the ability of myoglobin to scavenge NO [39] or, possibly, to prevent redox cycling [40]. Plasma endothelin-1 also increases; renal function can be improved by prior administration of an endothelin antagonist. Thromboxane A_2 receptor antagonists (TxRA) can also improve renal function in this model [41]. The F_2-isoprostanes are a group of prostaglandin-like compounds formed by the action of free radicals on arachidonic acid [42] (Fig. 4). The F_2-isoprostanes are good in vivo markers of lipid peroxidation and are themselves renal vasoconstrictors. They are markedly elevated in the glycerol model [43] and in human beings with rhabdomyolysis [44] (Fig. 5). TNFα has also been shown to be increased after injection of glycerol; the subsequent ARF can be partially ameliorated by prior administration of an anti-TNFα antibody [45]. This may possibly be due to a reduction in gut perfusion, with consequent increases in endotoxin and bacterial translocation leading to immune system activation.

Treatment of acute renal failure

Treating the muscle injury

Restoration of muscle blood flow by volume expansion may prevent more extensive muscle necrosis but, paradoxically, can transiently increase muscle damage by causing reperfusion injury [20].

Dantrolene (1 mg/kg i.v. bolus) or bromocriptine (2.5 mg bd p.o.) may be helpful in malignant hyperpyrexia or neuroleptic malignant syndrome by stabilising membrane calcium channels in the sarcoplasmic reticulum. Indeed, they have been used in this setting. There is therefore theoretical justification for use of these agents in at least some cases of rhabdomyolysis [46].

Ongoing muscle damage may occur in the compartment syndrome and may be inferred from a continued CK rise, or from a failure of the CK level to fall. Some advocate regular transcutaneous needle measurement of intracompartmental pressures, but this is not our clinical practice as it effectively creates an open compartment, thereby increasing the chance of infection. Doppler ultrasound flow measurements or indwelling intravascular catheters passed down into the compartment can be used to monitor perfusion pressure. Infection may lead to unrecoverable muscle damage that usually requires extensive débridement. Fasciotomy should be undertaken only as a last resort when compartment pressures exceed 40 mmHg [36].

Volume expansion

Early volume replacement represents the single most important treatment to prevent the development of ARF [47]. Numerous studies in experimental models and in human subjects show that a degree of intravascular volume contraction is more or less a prerequisite for the development of ARF [2] One small ICU study showed no difference in terms of renal outcome between volume expansion with saline alone and expansion with saline followed by addition of mannitol and bicarbonate [48]. Administration of large quantities of fluid to crushed casualties at the scene, even before full extrication has occurred, is recommended. However, care should be exercised when administering large amounts of fluid to the elderly or the very young. Some authors

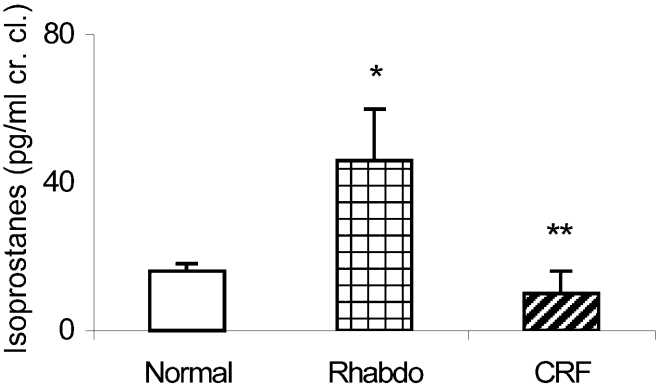

Fig. 5 Urinary isoprostanes were markedly elevated (*$p < 0.02$) compared with normals after rhabdomyolysis in human beings. Chronic renal failure *(CRF)* patients were used as a second control group with creatinine clearances similar to those of the rhabdomyolysis group *(Rhabdo)*. These patients had isoprostane excretions no different from those of normals and markedly less than those of patients with rhabdomyolysis (**$p < 0.002$). (Adapted from [37])

advocate using solutions containing 150 mmol/l sodium with 75 mmol/l chloride and 75 mmol/l bicarbonate; however, these are not readily available. In most cases, initial resuscitation does not require limitation of administered volume; alternating infusions of 0.9 % sodium chloride and 1.26 % sodium bicarbonate solutions can be used.

Alkalinisation

The traditional explanation that myoglobin toxicity is due to precipitation of myoglobin within the kidney was supported by the finding that myoglobin infused into experimental animals accumulates in the kidney more avidly in an acidic environment [49, 50]. Alkalinisation of the urine undoubtedly increases the solubility of myoglobin-THP complex and is accompanied by tubular washout of myoglobin casts. However, myoglobin can promote lipid peroxidation at concentrations of 1 μM, far below the mM level at which it precipitates. A considerable reduction in tubular concentration would be required to prevent these reactions. The recent finding that alkalinisation inhibits redox cycling of myoglobin and lipid peroxidation in rhabdomyolysis is clearly relevant [43] (Fig. 6). In isolated perfused kidneys metmyoglobin induced vasoconstriction only at acid pH [51]. Thus alkalinisation can improve myoglobin washout, prevent lipid peroxidation and renal vasoconstriction, and thus has much to recommend it as a therapeutic tool. Based on the pH at which redox cycling of myoglobin is reduced, it is our practice to give aliquots of alkali to keep the urine pH = 7.0.

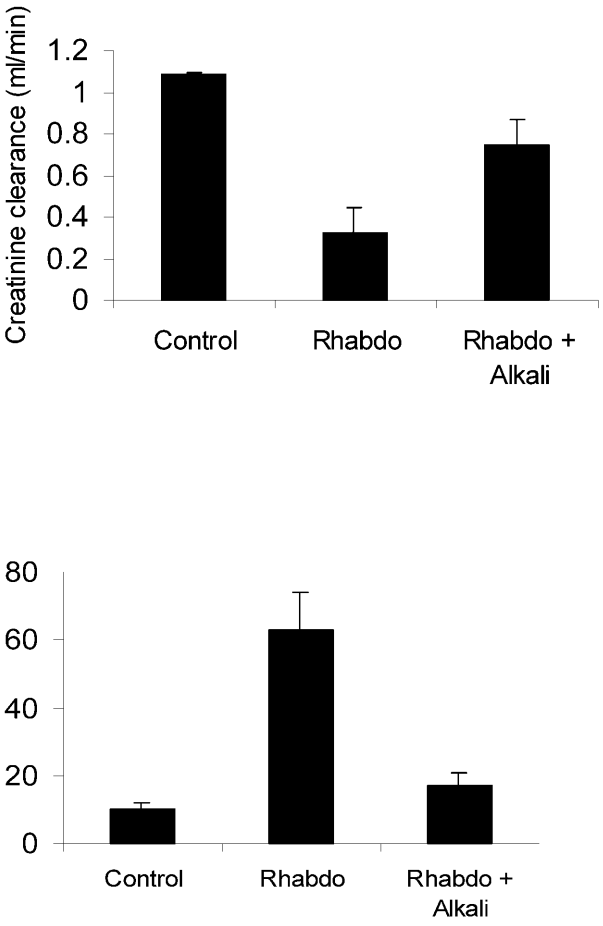

Fig. 6 Effect of alkalinisation on urinary F_2-isoprostane levels and creatinine clearance in a rat model of rhabdomyolysis

Mannitol

The use of mannitol is controversial. Its advocates point to its ability as an osmotic agent in promoting a diuresis which may reduce compartment pressures elevated due to muscle swelling [52, 53]. However, the addition of mannitol has not been shown to produce results superior to those of fluid expansion alone [48], and it may actually be harmful [54]. Mannitol also has weak antioxidant properties, but in the concentrations used here these are likely to be largely irrelevant [29]. It is therefore our practice to use this therapy only when it is aimed specifically at reducing compartment pressure.

Experimental therapies

Antioxidants

Haem-induced oxidant injury has emerged as one of the most important mechanisms of renal failure. As admin-

istration of antioxidants such as glutathione or vitamin E analogues improves renal function in experimental models [24], this may be a potentially promising approach in patients.

Physical therapies

There is no evidence that plasmapheresis improves outcome or reduces the myoglobin burden of the kidneys [55]. In a pig model of rhabdomyolysis given an intravenous infusion of myoglobin, continuous arteriovenous haemodialysis improved myoglobin clearance such that ~2 l was cleared per day; however, this was equivalent to ~10 % of the administered myoglobin [56]. Although haemodialysis, plasma exchange and haemodiafiltration increase myoglobin clearance, they have not yet been shown to confer any clinical advantage [57].

Charcoal haemoperfusion may be useful in the early stages of myoglobinaemia, but its superiority over alkaline diuresis has not been established. The complications, side effects and costs of this therapy make it unlikely that it will gain mainstream acceptance [55].

When to institute renal replacement therapy

The most important and life-threatening early complication of rhabdomyolysis is hyperkalaemia. This is best corrected by volume expansion and administration of isotonic sodium bicarbonate (1.26 %). Other methods of correction include salbutamol and insulin with glucose, but it is best to avoid calcium administration. If life-threatening arrhythmias are imminent and the methods outlined above are ineffective, dialysis or filtration is indicated. Uncorrectable acidosis is also an indication for dialysis, especially when this compromises the cardiovascular system. Exceptionally, if iatrogenic fluid expansion has occurred but the patient remains oliguric or anuric, fluid overload can be a problem. Pulmonary oedema is sometimes precipitated in this setting by the administration of mannitol. In these circumstances urgent dialysis is required. Dialysis has the advantage of correcting other metabolic abnormalities such as hyperphosphataemia, hyperuricaemia and hypocalcaemia. Since the acute renal failure is usually of rapid onset, correction of electrolyte and osmotic imbalances can also be rapid.

Although hypocalcaemia rarely causes a problem, it can occasionally cause cardiovascular compromise with hypotension and poor cardiac performance. Addition of calcium corrects these problems, but dystrophic calcification occurs. Thus dialysing initially against a low calcium dialysate will raise plasma calcium levels slowly, while ultrafiltration will remove excess phosphate.

Anticoagulation is best avoided if possible or, if continuous venovenous haemofiltration is necessary, pre- and post-dilution techniques should be used. Prostacyclin has theoretical advantages over heparin if anticoagulation is required.

Prognosis

It has been clearly shown that early volume resuscitation is the key to avoiding ARF. Of those surviving the Hanshin earthquake, only 25 % arriving in hospital within 6 h had ARF, compared with 100 % of those arriving after 40 h [58]. Patients with rhabdomyolysis-induced ARF who died after this earthquake had higher plasma levels of amylase, AST and LDH and CK levels > 75,000 U/l [59]. The causes of early (< 5 days) mortality were hypovolaemia and hyperkalaemia. Following anuric ARF due to rhabdomyolysis, renal function almost always recovers within 3 months if the patient survives [60]. However, the mortality from this condition is ~20 % [61].

Conclusion

Rhabdomyolysis is an important cause of acute renal failure for which new mechanisms of renal injury by haem-induced lipid peroxidation have recently been proposed. Reduction in renal blood flow and oxidant injury also appear to be important factors responsible for tubular injury. The haem group of myoglobin, as opposed to free iron, is likely to cause lipid oxidation; alkalinisation works by inhibiting the redox cycling of haem iron. Treatment strategies are aimed at correcting and controlling the potassium, restoring intravascular volume, and urinary alkalinisation. Future therapy is likely to be aimed at limiting oxidant injury.

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