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## Original Paper

# Rhabdomyolysis and Renal Function Impairment After Isolated Limb Perfusion—Comparison Between the Effects of Perfusion with rhTNFα and a 'Triple-drug' Regimen

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**The aim of this study was to monitor serum and perfusate levels of myoglobin (MB) and creatine kinase (CK) during isolated limb perfusion (ILP) in order to identify those at risk of renal failure. We investigated the release of MB and CK in 40 patients who underwent ILP for melanoma ($n = 15$) or sarcoma ($n = 25$) using rhTNFα/melphalan ($n = 28$) or a triple-drug regimen ($n = 12$). Serial determinations of CK and MB were performed in both perfusate and systemic circulation during and after ILP and renal function was assessed. A significant increase of MB could be detected in the perfusate during ILP. After ILP, an up to 100-fold increase with a double peak of MB at 4 h and 24 h postoperatively was observed. The maximum elevation of serum activity of CK was at 30 h. The increase for both proteins was highly significant ($P < 0.001$). ILP with rhTNFα/melphalan yielded significantly ($P < 0.001$) higher serum values of MB and CK and also the impairment of the renal function was more pronounced. The peak values of MB after ILP occur early and allow the patients most at risk of developing renal failure to be identified. Rhabdomyolysis can be detected early by determination of MB from the perfusate. Further measurements twice daily for 2–3 days post ILP from serum samples as well as daily assessment of MB in the urine is helpful for detecting myoglobinuria and imminent renal failure.** © **1997 Elsevier Science Ltd. All rights reserved.**

**Key words: isolated limb perfusion, rhTNFα, toxicity, myoglobinuria, rhabdomyolysis**

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## INTRODUCTION

ISOLATED LIMB perfusion (ILP) is a method of treating malignant melanoma and sarcoma with high dosages of cytostatic drugs and minimising the systemic side-effects [1]. Postoperatively, oedema, erythema and cutaneous necrosis can develop in the perfused limb. These complications are easy to assess and form the basis of the Wiederdink classification of toxicity [2]. However, severe rhabdomyolysis can also be induced by ILP, representing grade IV–V toxicity.

Recently, rhTNFα (TNF) was introduced to perfusion treatment and yielded high response rates in melanoma and sarcoma patients [3, 4]. The major limitation of TNF is considered to be induction of a 'septic shock-like syndrome' with pulmonary insufficiency in case of leakage from the perfusion circuit to the systemic circulation [5]. However, few data have been reported on regional toxicity in the perfused limb in comparison with ILP with cytostatic drugs.

Skeletal muscle injury releases cellular components such as myoglobin (MB) and creatine kinase (CK). Postoperatively, myoglobinaemia can result in a crush-kidney syndrome and several case reports concerning acute renal failure after ILP have been published [1, 6–9]. However, no analysis of the release of CK and myoglobin to the perfusate during ILP and to the systemic circulation after ILP has yet been reported.

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The aim of our study was to monitor serum values of MB and CK as a marker of skeletal muscle damage during and after ILP and to identify those patients with an increased risk of renal failure.

## PATIENTS AND METHODS

From April 1993 to January 1995, we studied 40 patients (20 males, 20 females) undergoing ILP for melanoma ($n = 15$) or soft tissue sarcoma ($n = 25$) with an age range of 22–76 years (median 52 years). ILP was carried out in 10 patients in the upper limbs and in 30 patients in the lower limbs.

In 28 patients, we used TNF as reported [3, 10]. In the upper limb the TNF dose was 3 mg and in the lower limb 4 mg combined with melphalan 10 mg/l perfusing limb volume. In 12 patients with soft tissue sarcoma, we applied a 'triple-drug' combination (cisplatin, melphalan and doxorubicin) as described earlier [11]. The perfused limb volume was measured using the displacement method in a water bath. After cannulation of the vessels, hyperthermic extracorporeal circulation was established through a heart–lung machine (Stöckert, Munich, Germany) and a Bentley®-Bubble-Oxygenator (Baxter, Munich, Germany). The perfusate temperature was 41–43 °C and the mean tumour tissue temperature 38.9 ± 0.7 °C. The drugs were applied at a tumour tissue temperature of 38 °C for 90 min (TNF) or 60 min (triple-drug). The perfusate volume was kept constant at approximately 700 ml during the perfusion. Oxygenation of the perfusate was determined by means of blood gas analysis. The scale of the systemic crossing of perfusate (leak rate) was indicated with autologous $^{111}$In-labelled erythrocytes and with $^{99m}$Tc-labelled albumin [12]. The median leakage rate was 0% in the TNF group (mean 2 ± 4%) amd 2% in the 'triple-drug' group (mean 8 ± 16%). The perfusate was rinsed with hydroxyethyl starch until no further reduction in the radiopharmaceutical activity was possible in the limb. At the end of the rinsing phase, the median residual $^{111}$In activity that could not be washed out of the perfused limb was determined to be 40% (range 8–90%, mean 43.4 ± 21.3%).

CK and MB were determined pre-operatively from central venous blood samples after insertion of all catheters (peripheral and central venous, urinary bladder), but before any kind of surgical treatment. During perfusion, samples from the perfusate and from the central venous catheter were obtained simultaneously every 15 min. Postoperatively, CK and MB were determined from central venous serum samples every hour for 8 h, every 2 h until 16 h, every 4 h until 48 h, and so on until it was only necessary to measure once every 24 h if the serum level continued to be high. The serum samples were stored at −20 °C.

Serum MB levels were established by nephelometry (Behring- Werke, Marburg, Germany), and CK was measured as enzyme activity (Beckman, Los Angeles, California, U.S.A.). In men, the normal values in the serum are 80 U/l for CK and in women 70 U/l; for MB they are 76 µl and 64 µl, respectively. To quantify the release of MB and CK, the serum concentrations were compared to the perfused limb volume ($MB_{vol}$ or $CK_{vol}$).

Postoperatively, every 8 h, cumulatively sampled urine was taken to determine the concentration of MB. The extent of myoglobinuria was calculated from the volume of urine produced in the same period and the values were summarised for 96 h. Every 12 h, creatinine clearance and serum concentrations of creatinine and urea were measured for at least 6 days in 35 patients. Diuresis with a urinary volume >4000 ml/24 h and urinary alkalisation (pH >6.5 using bicarbonate) was maintained to prevent renal failure. The clinical toxicity of ILP was classified after Wiederdink [2]: no skin reaction (grade 1), redness (grade 2), blisters (grade 3), superficial necrosis (grade 4), necrosis requiring amputation (grade 5).

For the statistical analysis we used paired *t*-tests, variance analysis, the Mann–Whitney *U*-test and Spearman's rank correlation to compare toxicity. Mean values are given as mean ± S.D., median values are given with their range. All calculations were performed with the SPSS program (SPSS Inc., Chicago, Illinois, U.S.A.).

## RESULTS

ILP was carried out as outlined in the protocol in 37 patients, but had to be interrupted in 3 patients under TNF perfusion after 45, 50 and 60 min because the cumulative leak rate reached 10%. All perfusions using the TNF regimen were performed without major complications [10]. The maximum toxicity in the perfused limb ranged from Wiederdink level I to level IV (6 patients at level 1, 22 patients at level II, 9 patients at level III, 3 patients at level IV).

### *Pre-operative measurements*

The mean and median pre-operative values were within the normal range (Table 1), but 8 patients had increased

*Table 1. Concentrations of MB (µg/l) and CK (U/l) systematically and in the perfusate pre-operatively and during ILP (mean ± S.D.)*

| | | Pre $n = 40$ | ILP 15′ $n = 40$ | 30′ $n = 40$ | 45′ $n = 40$ | 60′ $n = 38$ | 75′ $n = 25$ | 90′ $n = 25$ | Start ILP versus end | Pre-ILP versus end |
|---|---|---|---|---|---|---|---|---|---|---|
| MB | System | 65 ± 99 | 51 ± 54‡ | 48 ± 53‡ | 44 ± 50‡ | 40 ± 46‡ | 41 ± 46‡ | 38 ± 49‡ | $r = 0.90$ $P < 0.005$ | $r = 0.88$ $P < 0.01$ |
| | Perfusate | N/A | 65 ± 71 | 69 ± 78 | 75 ± 87 | 85 ± 95 | 99 ± 116 | 128 ± 156‡ | $r = 0.84$ NS | $r = 0.91$ $P < 0.05$ |
| CK | System | 44 ± 56 | 44 ± 52 | 43 ± 53 | 41 ± 52 | 44 ± 54 | 50 ± 61 | 55 ± 65 | $r = 0.98$ NS | $r = 0.98$ NS |
| | Perfusate | N/A | 34 ± 62† | 33 ± 60† | 32 ± 58† | 34 ± 61† | 41 ± 66 | 42 ± 70 | $r = 0.99$ NS | $r = 0.98$ NS |

†$P < 0.01$; ‡$P < 0.05$; comparison of values during ILP with pre-operative values by Student's *t*-test ($P$); correlation between pre-ILP or the start of ILP values versus end of ILP (Spearman's coefficient, $r$). NS, not significant.

CK values (max. 253 U/l), and 15 patients had increased MB values (max. 410 μg/l).

*Changes during ILP (Table 1)*

*Myoglobin.* At the beginning of ILP, MB was significantly lower ($P < 0.05$) than the pre-operative values in the systemic circulation, and during ILP the systemic values continued to fall significantly ($P < 0.05$). In the perfusate, the values of MB increased significantly compared with those at the start of perfusion ($P < 0.05$).

*Creatine kinase (Table 1).* After starting and during ILP, no significant changes were observed in the systemic circulation. The CK values in the perfusate were significantly lower ($P < 0.01$) at the beginning of ILP in comparison with the pre-operative systemic value, but the level rose towards the end of the perfusion (75–90 min) to pre-operative levels.

*Alterations after ILP*

*Myoglobin.* Postoperatively, we observed very different individual courses of the serum protein levels and the differences for MB were greater than those for CK. Maximum values of less than 200 μg/l MB were detected in 10 patients and values of more than 1000 μg/l in 15 patients. In 13 cases, there were two peaks: in 5 patients the second peak was higher than the first; in a single patient both peaks were equal; and in 7 patients the first was higher than the second. In these 13 patients, the first MB peak appeared after a median of 4 h with a mean of $2906 \pm 474$ μg/l and a second peak after a median of 24 h with $8748 \pm 2696$ μg/l. In 26 patients the increase varied, 6 of them had a first peak later than 24 h postoperatively. For all patients, there was a significant increase in the mean value ($P < 0.05$) in MB 1 h after reperfusion (Figure 1a). The median time lapse from the end of perfusion to the absolute individual maximum for all patients was 14.7 h (3–38 h). The maximum value of MB (98–220 μg/l) was observed in the patient who died 72 h post ILP. Without taking his values into calculation, the mean maximum value was $2209 \pm 5588$ μg/l.

*Creatine kinase.* A moderate increase with maximum values below 200 U/l was measured in 10 patients while another 20 patients showed serum concentrations that exceeded 1000 U/l. In 11 cases, the CK serum values peaked twice: in 7 patients the second peak was higher than the first, in 3 patients both were approximately equal and in 1 patient the first peak was higher than the second. In these 11 patients, CK first peaked at $451 \pm 484$ U/l after a median of 12 h and peaked again at $1354 \pm 2033$ U/l after 47 h. In the 27 patients remaining, a slow increase was found in the early postoperative course. At 1 h after reperfusion, a significant increase ($P < 0.05$) compared with the pre-operative values was observed in all patients (Figure 1b). The median time lapse to the absolute individual maximum for all patients was 30.2 h (1–134 h) and the mean maximum value of CK was $1335 \pm 2245$ U/l.

*Correlation between CK and MB at different time points during ILP*

Pre-operative values of CK and MB and those during ILP, both systemic ($r > 0.63$, $P < 0.001$) and in the perfusion circulation ($r > 0.87$, $P < 0.001$), were significantly correlated. There was also a correlation between the maximum values postoperatively ($r = 0.63$, $P < 0.01$). The maximum for MB occurred earlier, after a median of 14.7 h, in comparison with the peak of CK, after 30.2 h ($P < 0.001$).

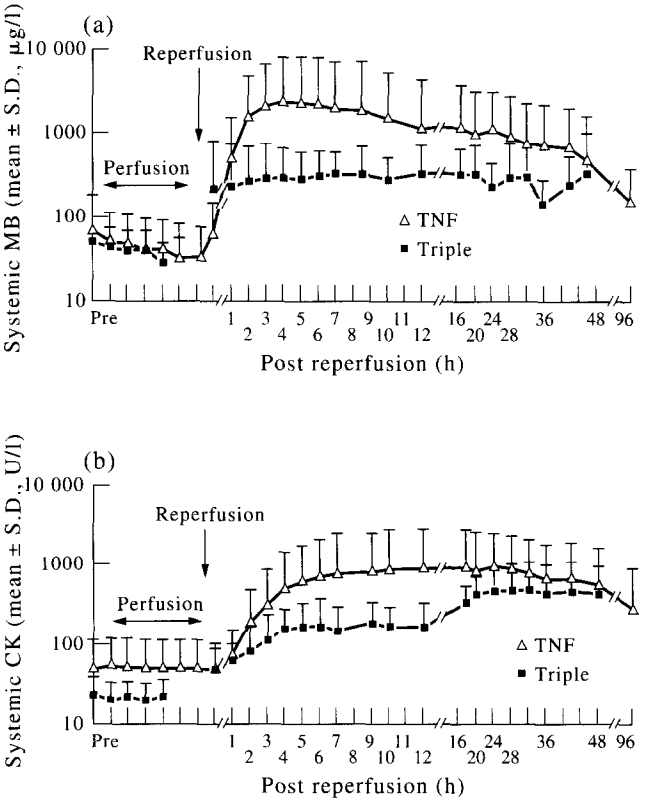


**Figure 1. Time course of CK and MB during and after ILP in the perfusate and systemic circulation comparing perfusion with rhTNFα/melphalan (triangles) and a triple-drug regimen (squares). Postoperative peak values are higher after TNF perfusion ($P < 0.01$ for MB; $P < 0.02$ for CK). Note the earlier occurrence of MB peak values ($P < 0.01$, ↓ = onset of reperfusion after ILP, log scale)**

*Correlations between pre-, intra- and post-ILP values*

There were no significant correlations between the maximum peaks post-ILP and the pre-operative CK or MB activities ($r = 0.32$, $P < 0.1$). There was a significant correlation between the peak ($r = 0.91$, $P < 0.001$) or time point ($r = 0.38$, $P < 0.05$) of the maximum peak and the MB concentrations determined 5 min after reperfusion, which could not be demonstrated for CK.

*Correlations to parameters of ILP*

Several parameters of ILP were analysed for correlation with the course of MB and CK (Table 2). The maximum serum concentration of CK and MB correlated significantly with the perfused limb volume. In a multivariate Cox regression analysis these were the only significant variables (for CK: $P < 0.02$, beta 0.88; for MB: $P = 0.01$, beta 0.79). The clinical toxicity after Wiederdink showed no correlation to the leak rate or the residual activity of labelled erythrocytes, but we found a correlation between the clinical toxicity and the maximum tumour tissue temperature. The limb volume perfused correlated somewhat to clinical toxicity, but only for MB. The leak rate to systemic circulation and the residual activity of $^{111}$In-erythrocytes and $^{99m}$Tc-albumin within the limb after ILP showed no correlations.

*Table 2. Correlations between parameters of ILP and concentrations of MB and CK at different time points. The course of MB and CK was characterised by the concentration at the end of the ILP in the perfusate and systemic circulation by peak and time of the maximum peak. In addiiton, the maximum serum concentrations of MB and CK were compared to the perfused limb volume and the parameters mentioned*

| Parameters of ILP | | Concentrations of MB and CK at | | | | |
|---|---|---|---|---|---|---|
| | | End of ILP systemic | End of ILP perfusate | Maximum serum level | Time of max. | Maximum (corrected*) |
| Toxicity | CK | | $r = 0.40$; NS | $r = 0.03$; NS | $r = 0.12$; NS | $r = 0.24$; NS |
| | MB | | $r = 0.32$; NS | $r = 0.39$; $P < 0.04$ | $r = 0.09$; NS | $r = 0.47$, $P < 0.05$ |
| Max. tissue temperature | CK | | $r = 0.34$; NS | $r = 0.20$; NS | $r = 0.09$; NS | $r = 0.20$; NS |
| | MB | | $r = 0.20$; NS | $r = 0.38$; NS | $r = 0.08$; NS | $r = 0.36$; NS |
| Leakage rate | CK | $r = 0.08$; NS | | $r = 0.13$; NS | $r = 0.13$; NS | $r = 0.30$; NS |
| | MB | $r = 0.09$; NS | | $r = 0.12$; NS | $r = 0.08$; NS | $r = 0.05$; NS |
| Limb residual | CK | | | $r = 0.27$; NS | $r = 0.17$; NS | $r = 0.24$; NS |
| $^{111}$In-activity after rinsing | MB | | | $r = 0.31$; $P < 0.1$ | $r = 0.05$; NS | $r = 0.27$; NS |
| Limb volume | CK | | | $r = 0.58$; $P < 0.05$ | $r = 0.21$; NS | |
| perfused | MB | | | $r = 0.62$; $P < 0.01$ | $r = 0.10$; NS | |

*Corrected for limb volume perfused. NS, not significant; $r$, Spearman's coefficient.

These data indicate that toxicity in terms of MB and CK release after ILP is not only a problem of the quantity of the muscle mass perfused.

*Perfusion with rhTNFα/melphalan versus the 'triple-drug' regimen*

The serum concentrations of MB and CK were compared between patients treated with rhTNFα or the 'triple-drug' regimen (Figure 1). There were significant differences in the postoperative serum levels of both proteins. Intra-operative concentrations in serum and in the perfusate were similar. The postoperative increase of MB serum levels occurred earlier in the TNF group, at a median of 6 h versus 24 h ($P < 0.01$), and was more extensive with peak values at $2674 \pm 6161$ µg/l versus $842 \pm 974$ µg/l ($P < 0.02$) in the group treated with the 'triple-drug' regimen. The maximum CK values also occurred earlier in the TNF group at a median of 24 h versus 45 h ($P < 0.001$) in the other group, but there was no significant difference between the peak values $1196 \pm 2116$ versus $1764 \pm 2556$ U/l (n.s.). A significant difference between both treatment regimens could be demonstrated 1 h after the perfusion for MB values and at 3 h for CK concentrations.

*Renal function after ILP*

Six days following his operation, a 65-year-old male died from multiple organ failure having received ILP for malignant fibrous histiocytoma with the triple-drug regimen. There was a leakage rate during ILP of 0.6% and after reperfusion, wash-out was reduced to 40% of the radiotracers. On the third postoperative day, he developed renal failure, and hepatic, cardio-circulatory and respiratory insufficiency followed. A dramatic increase of serum MB and CK was observed reaching a maximum 6 h before death (MB at 98 220 µg/l). This patient's data were excluded from further analysis.

In all patients, the renal function showed a tendency to deteriorate after ILP. Median serum creatinine levels increased until the third postoperative day and fell thereafter. Serum urea levels increased for 8–14 days, postoperatively. Creatinine clearance tended to decrease from the first to the fifth day, but pathological levels below 70 ml/min were measured in only 11 patients (9 patients after TNF, 2 patients after triple-drug treatment). The cumulative amount of myoglobinuria reached maximum values up to 145 g/96 h. There was a good correlation between $MB_{max}$ and $CK_{max}$ with the maximum levels of serum creatinine ($r = 0.51$), but only a moderate correlation between creatinine levels and cumulative myoglobinuria ($r = 0.35$). No significant correlation could be established for the serum clearance of creatinine. However, there was a strong correlation between myoglobinuria and $CK_{max}$ and $MB_{max}$ (Table 3).

## DISCUSSION

Hyperthermic isolated limb perfusion treats malignant melanomas and soft tissue sarcomas very effectively by delivering high concentrations of cytostatic drugs to the tumour [1, 11, 13, 14]. However, both local toxicity and systemic side-effects can appear after ILP with cytostatics and/or cytokines. Several authors have reported on intestinal ischaemia, acute renal failure or oliguresis with some lethal results [7, 8, 13, 14]. No clearly pathophysiological cause could be determined and endothelial damage was postulated as the underlying mechanism [9]. 5 patients in the literature have been definitely diagnosed as having crush syndrome after ILP with melphalan or cisplatin [7]. The authors proved in all patients a myoglobinaemia lasting over 36 h

*Table 3. Correlation between the serum parameters of MB and CK, myoglobinuria and renal function during 96 h post-ILP (r, Spearman's rank correlation)*

| | Serum creatinine | Creatinine clearance | CK max. | MB max. |
|---|---|---|---|---|
| *a: All patients (n = 35)* | | | | |
| CK max. | 0.61† | −0.11 | | |
| MB max. | 0.61* | −0.17 | | |
| Myoglobinuria/96 h | 0.35 | −0.10 | 0.69† | 0.58† |
| *b: Pathol. clearance only (n = 11)* | | | | |
| CK max. | 0.75* | 0.22 | | |
| MB max. | 0.72* | 0.24 | | |
| Myoglobinuria/96 h | 0.18 | 0.18 | 0.70* | 0.49† |

Crea, maximal serum concentration of creatinine; clearance, minimal creatinine clearance. (a) all patients; (b) patients with a pathological creatinine clearance in the postoperative period, *$P < 0.01$; †$P < 0.05$.

and in 2 patients a myoglobinuria. Further cases of myoglobinuria have been reported [1, 6, 15].

Our analysis provides data on the kinetics of myoglobinaemia and release of CK during and after ILP available. The peak levels we detected with rhTNFα/melphalan or melphalan + doxorubicin + cisplatin were higher than those reported when patients were examined at 24 h intervals [1, 15] and after ILP with melphalan or cisplatin alone—the maximum serum concentrations of CK occurred on the second postoperative day and normalised at days 4–5. Our serum kinetics indicate clearly that the elevation of MB preceeds that of CK by 12–24 h.

However, a significant increase of MB in the perfusion circulation can be detected at 90 min of perfusion time, indicating the onset of toxicity to the muscle cells. To our knowledge, no comparative data from other studies are available. The perfusate temperatures of 41–43°C, being slightly higher than normally used, might have contributed to the increased local tissue effect. After reperfusion, both MB and CK showed a slow increase, reaching a first peak in some of the patients. The serum concentrations then increased further, up to a maximum which appeared in MB on the first and in CK on the second postoperative day. The maximum peak reached was more than 100 times above the normal values.

Interestingly, the postoperative increase of MB and CK differed in patients after ILP with rhTNFα or the 'triple-drug' regimen. In the TNF group, MB and CK peaked earlier and the levels were significantly more extensive. This supports the thesis that the degree of rhabdomyolysis does not depend only on the muscle mass perfused, but is induced by specific mechanisms of cell damage. There is evidence of a TNF-induced proteolysis [16] and also endothelial activation could lead to a diminished perfusion of muscle cells resulting in structural damage [17].

The difference in time to the maximum serum values of MB and CK can be explained by the intracellular location of the proteins. Myoglobin is a low molecular weight protein (17.5 kDa) and is mostly cytosolic. After membrane damage, the protein can easily cross the interstitium into blood vessels. The myoglobin content of the muscle cells is very different per individual and this may account for the high interindividual variations observed in our patients. In comparison to MB, CK has a higher molecular weight (81 kDa) and is up to 50% particle-bound to the contractile system with a mitochondrial-bound pool. It will be released only if there is further structural loss of the skeletal muscle [18]. This accounts for the finding that the time of peak serum values of CK and MB were correlated, but the maximums were not. Obviously, in different patients, different levels of cellular damage were induced by ILP and our data indicate that ILP using TNF induces damage to the muscle cell membrane with release of MB in accordance with reports on higher membrane porosity [19]. In contrast, for cytostatic drugs such as doxorubicin and cisplatin, membrane damage and disruptions in the metabolism of the myocytes have been described [20]. The different rates of increase in the early and later phase after reperfusion indicate that two different mechanisms overlap each other. The early release of proteins from the skeletal muscle may also be influenced by the surgical trauma with extracorporeal circulation and soft tissue compression by a tourniquet [21].

The protracted release of muscle proteins after ILP leading to a second serum peak value for MB may occur due to oedema or an increased compartment pressure of the limb [22, 23]. After perfusion, free oxygen radicals could also be responsible due to the application of cytokines or cytostatic drugs and changes in the local calcium balance [24, 25]. In traumatic rhabdomyolysis, this has been called the "second-wave phenomenon" [21].

Rhabdomyolysis, with release of intracellular proteins, led to a massive myoglobinuria in some patients. Despite prophylaxis, the renal function was partially reduced in 26% of the patients without direct influence on myoglobinuria. Transient increase in creatinine and urea was an additional result of rhabdomyolysis and postoperative catabolism.

Myoglobinaemia can lead to tubule necrosis, producing a deterioration of the renal function causing even acute renal insufficiency. The precise mechanism has not been clarified. It is plausible that myoglobin precipitation in the acid urinary tract milieu, particularly simultaneous with dehydration, leads to obstruction of the tubuli and, as a consequence, to tubule necrosis. Myoglobin also directly influences glomerular filtration and renal blood flow via intrarenal vasoconstriction [20, 25]. In an acid milieu, myoglobin decays below a pH of 5.6 to the ferrous haem and a protein moiety, and the formation of a haem–uric acid complex and protein precipitates have been postulated [25]. Haem has a direct toxic effect on the tubule cells and may catalyse the formation of free radicals [24]. In non-traumatic rhabdomyolysis, the risk group of patients for acute renal insufficiency is characterised by high CK (>4000 U/l) and MB values (>1000 μg/l), acidosis and dehydration [21].

There have been several recommendations for the prophylaxis of crush syndrome, particularly in post-traumatic rhabdomyolysis. Urinary alkalisation with sodium bicarbonate leads to better solubility of myoglobin in the urine and, with simultaneous forced diuresis, can prevent myoglobin precipitation. Following studies in post-traumatic patients, urinary alkalisation (pH > 6.5) and forced diuresis (>200 ml/h) has been recommended [26–28]. So far, it has been standard to administer dopamine to mediate an improvement in renal function in postoperative prophylactic revascularisation [8, 29]. Further attempts to prevent reperfusion disease, such as radical scavengers, rinsing the limbs after reperfusion, nitric oxides and prostaglandin inhibitors, have been discussed, especially in vascular surgery [30, 31].

In our clinical setting, rhabdomyolysis induced by isolated hyperthermic limb perfusion with cytostatic drugs or cytokines will be detected earliest by determination of myoglobin in the perfusate at the end of ILP. Post ILP, serum determinations of MB and/or CK are performed twice daily for at least 2 days. If serum levels of CK or MB continue to be high (>500 μg/l or U/l), especially for MB, forced diuresis is continuously carried out until the concentration of MB is less than 500 μg/l or CK less than 1000 U/l for 48 h. A minimum urinary excretion of 4000 ml/24 h and alkalisation with a target urine pH > 6.5 are achieved. It should be borne in mind that ILP using rhTNFα not only bears the risk of a septic shock syndrome but also severe locoregional side-effects must be expected.

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