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Renal replacement therapy in crush syndrome

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Summary

Crush syndrome (CS) is defined as a severe systemic multi-organ failure resulting from a massive mechanical injury of skeletal muscles. It occurs after trauma, muscle compression during prolonged lying, alcohol poisoning, cocaine overdose, adverse effects of some drugs as well as bacterial, viral infections, hyperthermia, hypothermia and frostbite. The basis of pathophysiology is rhabdomyolysis i.e. increased permeability of damaged myocyte cell membrane, resulting in the release of toxic substances from muscle fibers cells into the bloodstream. It frequently leads to acute renal failure, hypovolemia and shock. Recognition of crush syndrome requires early fluid resuscitation, ICU treatment and implementation of Renal Replacement Therapy (RRT) simultaneously with urine alkalization. Continuous veno-venous hemofiltration (CVVH) is also recommended as it improves the transfer of filtered myoglobin molecules. A multitude of related clinical problems with various etiology, pathogenesis, courses as well as the complicated and multidimensional therapy contribute to the complexity of a presented problem. *Anestezjologia i Ratownictwo 2009; 3: 57-66.*

Keywords: rhabdomyolysis, myoglobin, acute renal failure, renal replacement therapy, haemodialysis, hemofiltration

Contents

Muscles comprise about 40% of the body weight and contain about 75% of total potassium. Therefore, it is commonly known that the consequences of massive muscle damage and other diseases resulting in their destruction are very dangerous.

The word „crush" is defined as pressing or squeezing two bodies resulting in injury or breaking. No wonder this term is often used in traumatology in order to define aetiology and/or mechanisms of various injuries, mainly accidents and disasters leading to massive and severe damage [1,2].

Crush syndrome was first reported in the German literature in 1881. The cause-and-effect relationship between injury as a crush factor and following acute renal failure was described in 1909 after the Messina earthquake in Sicily. However, the best sources of information on crush syndrome are the papers of two English scientists (Bywasters, Beall, 1941) from the times of II World War, in which they describe injuries of London bombing victims. A few reports appeared also in Japan after the atomic bomb explosion over Hiroshima and Nagasaki [1,3].

In the 80's of the 20th century research results devoted to pathophysiology of crush syndrome were published. Three theories were formulated (toxic, neuroreflective and plasma loss) and they explained

the mechanisms of systemic failures in rhabdomyolysis [4]. As the term crushed wound" refers only to injury, the term "crush syndrome" (CS-Crush Syndrome) is much wider. It describes severe, systemic consequences of mechanical damage to striated muscles [1].

Skeletal muscles are 100–1000 times more sensitive to tension and compression than skin. When they are excessively pressed, swelling and hypoxia appear, which results in necrosis and myocyte lysis and the release of their catabolites. The process is called rhabdomyolysis i.e. the rapid breakdown of striated muscles. Rhabdomyolysis is the basis for the pathophysiology of crush syndrome resulting from trauma as well as the damage following it [1,2].

Crush syndrome is mostly the consequence of extensive crushed wounds e.g. when people are crushed by falling walls in construction disasters, mine accidents, armed conflicts or natural disasters (earthquakes, hurricanes, typhoons, etc.). It is considered to be one of the most severe conditions, especially when it is combined with detonation and blow syndrome. It can be observed as a result of disequilibrium between energy produced and used by skeletal muscles. It also occurs in case of muscle compression during prolonged lying (e.g. coma, tight fascial compartment syndrome), status epilepticus, too exhausting physical exercise, myocardial infarction, alcohol poisoning, drug overdose: cocaine, heroine, amphetamine, as well as in hyperthermia and burns, hypothermia and limb frostbite. Among other causes of rhabdomyolysis we can distinguish: side effects of therapy with statin drugs, fibrate drugs, theophylline, cyclosporine A; muscular dystrophy, muscle inflammatory conditions, carbon monoxide poisoning, rhabdomyosarcoma and other malignant neoplasms infiltrating and destroying striated muscles, thrombotic/embolic disease, metabolic and electrolyte disorders, such as hypokalemia, hypophosphatemia, hyponatremia, diabetes, bacterial and viral infections, such as influenza A, mononucleosis, tetanus, sepsis, Legionnaires' disease, Rocky Mountains spotted fever. Intense and prolonged muscle compression results in ischemia and necrosis, which lead to local and systemic complications [1,3,5-7].

Removing a damage factor is necessary before implementing advanced rescue activities. They restore tissue metabolic activity, but inevitably lead to occurrence and intensification of complications. This a peculiar paradox evoked by a sudden release of metabolites of reactions occurring under anaerobic conditions in crushed muscles [6]. The consequence of crush syndrome is the increase of permeability of cell membranes of damaged myocytes and the release of toxic substances into the bloodstream. They include myoglobin, creatinine, potassium released during muscle breakdown. It is accompanied by decrease in calcium concentration in blood <8 mg/dl (<2 mmol/l), anion gap metabolic acidosis and a significant increase in potassium concentration (>6 mmol/l), uric acid >8 mg/dl (>475,8 μmol/l) and phosphates >8 mg/dl (>2,6 mmol/l). Concentration of creatinine in plasma and non-protein nitrogen in blood (BUN - Blood Urinal Nitrogen) may increase rapidly and reach the levels of >2,0 mg/dl (176,8 μmol/l) and >40 mg/dl (>14,3 mmol/l) [1,3]. During prolonged compression skeletal muscles are exposed to oxygen deficit, which results in increased lactate production, decrease in blood pH and occurrence of metabolic acidosis. Moreover, increase of activity of, so-called, muscle enzymes in serum is noted. The enzymes include: creatinine kinase (CPK), lactate dehydrogenase (LDH), aldolase, alanine and aspartate aminotransferase (ALAT) and (AspAT). Hepatotoxic adenine nucleotides are released from damaged muscles, which cause increased production of uric acid by a liver and marked hyperuricemia [3]. In the initial stage of crush syndrome hypocalcaemia occurs, which a result of Ca^{2+} ions is moving inside damaged muscle cells. A big amount of free calcium ions in myocytes causes increase of permeability of cell membrane to sodium and at the same time it increases the threshold of cell excitability. It also causes muscle fibre contraction that exhausts muscle energy resources. As the disease progresses hypocalcaemia intensifies due to irreversibility of calcium ion binding during calcific myonecrosis. However, during the recovery stage hypercalcemia can be observed, which is an effect of parathormone and the increased production of 1,25-dihydroxycholecalciferol. Hypercalcemia is more often observed in patients whose therapy included calcium supplementation, so the supply of calcium is recommended only in case of convulsions or cardiac arrhythmia caused by hypocalcaemia [2,6,7,8].

Myoglobin – a heme pigment – can be found in skeletal muscles and a heart muscle. It is similar to haemoglobin as it can also bind oxygen reversely and serves as its reserve source. Myoglobin has a molecular weight of 18800 Daltons and it accounts only for ¼ of haemoglobin weight. Therefore, it is small enough to

permeate through renal glomerular vessels to uriniferous tubules. In case of chronic hypoxia the amount of myoglobin in muscles increases. Its presence in urine indicates significant muscle damage. It is assumed that the breakdown of about 200 g of muscles may result in myoglobinuria [1,3]. Normal myoglobin concentration is estimated at 10-46 μg/l (28-72 ng/ml). Renal threshold is 15 mg/100 ml. When myoglobin concentration in plasma reaches the level of 0,03 mg/dl, filtration takes place in renal corpuscles. In acid plasma and urine environment a myoglobin ion is transformed from anion to cation. Then the conversion to acid ferrohematin takes place and it reacts with Tamm–Horsfall proteins. It causes precipitation of conglomerates in proximal tubules and as a result their obturation [1]. Myoglobin shows nephrotoxic activity when it affects tubular epithelial cells. Moreover, it shrinks renal vessels, which additionally reduces filtration ability and leads to acute renal failure (ARF - Acute Renal Failure) [3]. This is a pathologic condition characterised by a sudden decrease in urination, which does not allow removing toxic products of metabolism. In majority of cases it does not exceed 50 ml a day [9,10]. Research shows that acute renal failure occurs together with metabolic acidosis and when urine pH is <6 [1]. Hypovolemia and reduced flow of blood in renal tubules intensify renal damage. Renal failure can be prevented by urine alkalization (pH >6,5) and implementing forced diuresis [1,3]. Myoglobin that is filtered into Bowman's space is reabsorbed in proximal tubules. Porphyrine ring is metabolized in tubular cells and Fe^{2+} ions are freed. In physiological conditions free iron is quickly bound by ferritin and ferroprotein complexes are created. In rhabdomyolysis, however, when big amounts of ionized iron are freed to uriniferous tubule lumen, exhaustion of enzymes is observed. Fe^{2+} cations, through free radical catalysis during lipid oxidation, inactivate intravascular nitrogen oxide NO, which results in blood vessel contraction. This phenomenon is intensified when it is accompanied by hypotension and hypovolemia [1,3]. Remarkable amounts of thromboplastin, which is present in circulatory system, generate intravascular coagulation together with thrombuses in renal corpuscles [7,9]. Rhabdomyolysis activates freeing of proinflammatory mediators and hormones, such as angiotensine II, endoteline, tromboxan – A_2, vasopresine and catecholamine. It also contributes to intensification of hypovolemia and renal vessel contraction, and thus it decreases renal filtration [1].

The pathogenesis of crush syndrome should be considered on the basis of two processes: rhabdomyolysis and acute renal failure resulting directly from it. Significant loss of plasma in the course of skeletal muscle crush (amounting even to 10 litres per damaged limb) reduces circulating blood volume, condenses it and leads to hypovolemia and shock. Blood is saturated with products that are normally excreted, such as urea, bilirubin, potassium and phosphorus. Urea is the main end product of protein metabolism. About ½ of urea filtered in renal corpuscles is absorbed reversibly in kidneys, the rest is excreted with urine. Urea nitrogen accounts for 50% of non-protein nitrogen, and in renal failure even for 95% [1].

Pain irritation, caused by reflex contraction of blood vessels, induces dysfunctions of respiratory and circulatory systems. Pain disrupts functions of respiratory and circulatory systems. Frequently reported symptoms are: reflex contraction of blood vessel, decrease in diuresis, blood condensation and decrease in immunity as well as sensitiveness to blood loss. Electrolyte disorders and hypovolemia are the main causes of acute heart failure [5].

During reperfusion in damaged skeletal muscles leukocytes with polymorphic nuclei are accumulated and they pour into the bloodstream. They produce free radicals and secrete myeloperoxidase i.e. enzyme catalizing reactions producing potentially cytotoxic oxidants of hypochloraus acid and N-chloramine. The presence of activated neutrophilic granulocytes may also result in damaging epithelial cells because they produce active oxygen metabolites: peroxides and hydro-oxygen radicals, which increase permeability of surface epithelial layer. Leukocytes with polymorphic nuclei pay a very important role in multi-organ damage caused by reperfusion [1,6].

All pathogenic mechanisms in crush syndrome are reciprocally intensified and affect negatively the whole organism. When a patient survives a shock caused by trauma, crush syndrome symptoms appear after a few hours after action of inducing factor. Initially general condition of injured people is good. Clinical picture develops slowly and it resembles a post-traumatic shock but it is not the case. There are three stages of crush syndrome: early, intermediate and late. In an early stage, which lasts 3-4 days after trauma, oedema and lividity of an injured limb or other part of the body are observed. Bladders filled with serous or serosanguineous liquid appear on the skin. In peripheral parts

of a limb filiform pulse and increased pulse rate are noted, after some time it becomes impalpable. Arterial blood pressure decreases to about 80/60 mmHg. If crush syndrome exacerbates, patient's condition deteriorates. Patient becomes apathetic, reacts poorly to the surroundings, nausea and vomiting appear. Blood coagulability is disturbed. From the 2nd or 3rd day of post-traumatic circulation decompensation increase in thrombotic readiness is observed, which is a result of penetration of excessive amount of tissue thromboplastin. It includes: decrease in free heparin concentration, increase in plasma tolerance to heparin and increase in plasma fibrinogen concentration. Urine is dark red and sediment contains albumins, erythrocytes, haematin, myoglobin and granular casts [1,4,8].

In the intermediate stage, during which both improvement and deterioration can be observed, oedema of crushed limb exacerbates, causing severe pain. Apparent improvement may occur in spite of observed oliguria. Intensive medical treatment and renal replacement therapy conducted at this stage may equalize kidney activity 8-12 days after the trauma. From the 7th day hypocoagulation condition develops, which results from consumption of blood coagulation factors in the body. This condition leads to disseminated intravascular coagulation (DIC – Disseminated Intravascular Coagulation) and thrombosis of small blood vessels of internal organs. In venous blood, especially the blood flowing away from site of crush, a marked change in parameters related to acid-base equilibrium is noted. Then blood pH decreases from 7,05 (directly after crush) to 6,87 in the sixth hour. Alkaline deficiency amounts to 6,6-21 mmol/l, which causes acidosis in ischemic tissues after crush. From the very beginning it resembles metabolic acidosis that intensifies markedly during a sudden decompression of a swollen limb or other parts of the body. Accompanying symptoms of infection in the site of trauma greatly deteriorate the prognosis [1,6,8].

In the late stage of crush syndrome (from 10-20 to 45-60 days after trauma) after controlling acute renal failure and without noticing any septic or respiratory complications, clinical picture shows prevailing local regressive symptoms of crush syndrome. They include: oedema, limb movement restriction, dysesthesia, muscular atrophy resulting from primary injuries. Generally, patients who survived the intermediate stage of crush syndrome, have good chance of recovery [1,5,6].

Clinical picture is strictly related to patient's general condition, strength and duration of crush trauma, as well as to damage of internal organs, blood vessels, nerves, fractures and others [5]. The pace of crush syndrome development is reversely proportionate to the time of proper therapy implementation and it depends on the kind of applied treatment. Bad prognostic factors that deepen pathology of rhabdomyolysis are severe infections, sepsis, multiple organ dysfunction (MODS – Multiple Organ Dysfunction Syndrome), disseminated intravascular coagulation (DIC), hyperphosphatemia and hyperuricemia [1,7]. In case of lack of help or its inefficiency majority of seriously ill patients die due to severe heart failure. In less serious cases circulatory disturbances may be minor and pass unnoticeably [6,8].

Prehospital procedures include maintaining victim's vital functions and preventing complications and crush syndrome occurrence. Rapid initiation of fluid replacement is necessary to maintain functions of circulatory system and to counteract hypovolemia. Immediately after releasing a victim, if not possible earlier, it is required to insert a cannula into peripheral vein and transfuse 0,9% NaCl or Ringer's solution in volume of 1500 ml/an hour. Shock-controlling procedures include also application of analgesics. Recognition of crush syndrome indicates rapid implementation of shock-controlling procedures and renal replacement therapy, simultaneously with urine alkalization [3]. It is very important to continue fluid replacement therapy. Fluid losses can be remarkable, e.g. in case of a limb they may amount to 10 l. It is a result of fluids moving inside damaged muscles. Fluid replacement therapy undertaken at a site of accident allows complementing intravascular volume, which is prophylaxis against acute prerenal failure. It is crucial to keep a positive fluid balance during first 2-3 days of treatment i.e. provide about 12 litres of fluid per day. During such intense hydration it is necessary to measure central venous pressure or pulmonary capillary wedge pressure (PCWP). Fluids administered intravenously should be supplemented with sodium bicarbonate ($NaHCO_3$) in dose of 100 mmol/l due to the risk of severe acidosis and accompanying hyperkalemia. Sodium bicarbonate is not only used in treatment of metabolic acidosis, but it also alkalizes urine. Maintaining urine pH at $\geq$ 6,5 enables to avoid formation of uric acid crystals and moreover, it increases dissolution of myoglobin, inhibiting precipitation and deposition of its conglome-

rates in uriniferous tubules [3]. Administering sodium bicarbonate potentially exposes a patient to the risk of metabolic alkalosis, which causes precipitation of calcium-phosphate concrements. It can be regulated with acetazolamide; its application may be required when pH > 7,45. However, the risk of metabolic alkalosis is less dangerous than acidosis, hypokaliemia and kidneys deprived of protection against toxic effect of myoglobin and uric acid [3,6].

A drug considered to be effective in ARF prevention in rhabdomyolysis is mannitol [3,6].

Having a variety of uses it is protective against crush syndrome complications. It induces movement of intravascular and extracellular fluid, which reduces blood viscosity and greatly improves kidney perfusion. Mannitol prevents contraction of renal vessels and as an osmotic diuretic it reduces oncotic pressure and increases intraurethral pressure, at the same time increasing glomerular filtration. It also prevents renal tubule blocking, myoglobin precipitation, pigmented cast formation as well as it reduces endocytosis and heme uptake in proximal renal tubule. It demonstrates cytoprotective action because it increases uptake of free radicals, not inhibiting their production. Mannitol shows also positive extrarenal action, e.g. decrease in muscle oedema, increase in mean arterial pressure and improvement of cardiac muscle contractility. Mannitol administration is recommended when diuresis is maintained at 4 l/a day. Mannitol as an osmotic diuretic does not lower urine pH [3,10].

Administration of loop diuretics is not recommended. They may induce dehydration and urine acidification – conditions that should be prevented during the whole treatment process [10].

Table 1. Recommended composition and volume of intravenous infusion fluid administered in crush syndrome. The procedure corrects hyperkalemia and prevents acute renal failure.

Glucose 5%	1000 ml
$NaHCO_3$	100 mmol
NaCl	140 mmol
Mannitol 20%	10 g
24-hour fluid supply:	12 litres
24-hour diuresis:	8 litres

To prevent acute renal failure in crush syndrome maintaining pH >6,5 is recommended.

The effective method of treatment and preventing acute renal failure in rhabdomyolysis is renal replacement therapy [3]. Indications for renal replacement therapy are:

- oliguria (200 ml/12 hours)
- anuria (do 50 ml/12 hours)
- increase in urea concentration >35 mmol/l.
- increase in creatinine concentration >400 μmol/l.
- increase in potassium concentration >6,5 mmol/l or its rapid rise
- increase in sodium concentration >160 mmol/l or its decrease <110 mmol/l.
- pulmonary oedema not responding to diuretic agents
- decompensated metabolic acidosis (pH >7,1).
- severe uraemia (encephalopathy, miopathy, uremic neuropathy and pericarditis).
- body temperature >40° C.
- intoxication with toxins that can be removed during dialysis.

Renal replacement therapy should be considered when one of the criteria mentioned above occurs, but it should be implemented immediately when two of them are observed [11]. Two main assumptions of renal replacement therapy are removing excess of fluids (water) and toxic substances they contain (acid metabolites, urea, potassium, etc.) [11].

Classic haemodialysis is based on two physicochemical principles. The process responsible for removal of excess body water is called ultrafiltration and it is based on the difference between transmembrane pressure at both sides of semipermeable membrane (analogically to physiological glomerular filtration). The rate of ultrafiltration depends on the difference in hydrostatic and oncotic pressure. As plasma water is filtered, oncotic pressure increases because plasma protein concentration rises. This phenomenon plays a remarkable role in case of related methods, such as hemofiltration and hemodiafiltration [10,12]. Removing toxic substances (endo– or exogenous) from intrasystemic fluids is called diffusion and its driving force is the difference between blood pressure and dialysis fluid at both sides of dialysis membrane [10,12]. The rate of diffusion (according to Fick's law) depends on molecular mass of dissolved substance, type of protein bonds, size of semipermeable membrane pores, the rate of blood and dialysis fluid flow and intermembrane pressure gradient [11,13]. In standard low-flux cellulose membrane medium-sized molecules or those

with molecular mass bigger than 500 Daltons cannot be filtered. High-flux synthetic membranes enable removing substances with molecular mass between 20000–40000 Daltons. The rate of diffusion of water solutions of non-protein substances with molecular mass below 5000 Daltons depends on the type of dialysis membrane, its permeability [11,13]. The bigger difference between pressure of solutions at both sides of membrane, the bigger transmembrane transport. Ideal membrane should be strong, thin (enabling maximum diffusion transport), high-flux type, with sieving coefficients that allow diffusion combination (removing small molecules) and convection (removing medium-sized and big molecules). Another characteristic feature should be high biocompatibility (lack of complement activation, granulocytes mobilization, thrombus formation) [6,14,15].

Hemofiltration is a method of extracorporeal blood purification based on removing water and water-soluble substances by convective transport through high permeability membrane. Convective transport is induced by minus pressure outside hemofiltration membrane. In spite of the fact that hemofiltration is a less effective method of removing solutions (because of decreased rate of fluid removal than during dialysis), it is an appropriate method to eliminate big molecules with mass above 25000 Daltons. During hemofiltration it is necessary to infuse substitute fluid composed well-suited for a patient's blood in order to avoid excessive loss of water and electrolytes [11]. The advantage of this method is that it is a process analogical to glomerular filtration taking place in physiological conditions. It is better tolerated because it does not evoke sudden shifts in homeostasis caused by haemodialysis. It is possible due to the rate of toxin elimination spread in time and correction of water-electrolyte moves. Heparinization of blood flowing through hemofilter is also lower than during haemodialysis due to modern construction of hemofilter membranes [6,11].

Membranes used in devices working in extracorporeal circulation must meet two requirements: they must clear blood of toxic substances and show durability in long-term contact with blood. There are two typical techniques of membrane production: modifications of natural substances, e.g. cellulose derivatives and chemical synthesis and polymerization of organic substances, as a result of which the following membranes are created: synthetic polyacrylonitrile membranes (Hospal, Asahi), polyamide (Gambro), polysulfone - polysulphonic (Fresenius, Amicon), polymethylomethacrylate. Chemical composition of polymer membranes is a crucial factor that can modify the level of purifying plasma of appropriate substances. Moreover, it is a key parameter indicating biocompatibility. Synthetic membranes are much more compatible than traditional cellulose material. Hemofiltration using synthetic membranes provides more detoxification opportunities in comparison to cellulose membranes because the size of synthetic membrane pores enables elimination of big molecules, even up to 5000 Daltons. Membrane characteristics do not depend only on chemical composition of polymer, but also on its microscopic structure. There are membranes with asymmetric micropore structure which are widely used in hemodialyzers as well as membranes with homogenous density. Effective clearance of small molecules, e.g. urea, should be conducted without excessive fluid consumption. Dialyzer membrane must enable purifying plasma of protein with a molecular mass of 10–40000 Daltons. Hemofilter must meet other requirements, such as appropriate resistance to transmembrane pressure differences of 300–400 mm Hg (40–50 kPa) and resistance to sterilization agents (ethylene oxide, gamma radiation, heat, etc.) [6,13-15].

In crush syndrome continuous hemofiltration is recommended as its main function is connected with the efficiency of transfer of filtered myoglobin molecules through membrane [13]. Haemodialysis and ultrafiltration cannot effectively eliminate myoglobin molecule out of blood [3]. Continuous Renal Replacement Therapy (CRRT) was initially applied to patients with positive fluid balance. It is the most effective method of treating critically ill patients with acute renal failure, for whom intermittent haemodialysis is difficult to apply because of their hemodynamic instability. High-permeable membranes used n continuous hemofiltration must have cutting off threshold for molecules of between 20000–50000 Daltons, low resistance to water, securing blood flow of 50-150 ml/min. (UF ± 500 ml/min.) [13,15].

Among continuous techniques we can mention the following: continuous veno-venous hemofiltration (CVVH) and continuous arteriovenous hemofiltration (CAVH), both based only on ultrafiltration and continuous veno-venous hemodiafiltration (CVVHDF) as well as continuous arteriovenous hemodiafiltration (CAVHDF), based on both ultrafiltration and diffusion. There are also methods based on slow ultrafiltration

and diffusion, such as continuous veno-venous hemodialysis (CVVHD) and continuous arteriovenous hemodialysis (CAVHD). Another method is also slow continuous ultrafiltration (SCUF) [11,12].

Continuous techniques were described for the first time in 1977. Since then they have been vastly modified and improved. Nowadays they are the most popular form of renal replacement therapy in European intensive care units. In continuous arteriovenous hemofiltration (CAVH) blood flow through hemofilter is induced by spontaneous arterial blood pressure (mean blood pressure should be higher than 70 mm Hg). Difference between arterial and venous pressure is a driving force for the blood flow through the filter [12]. The necessity of cannulation of arterial and venous vessel (most often femoral vein and artery) with 8 F catheter was accompanied by frequent complications and 15–20 percent mortality. During this procedure about 10 litres of fluid can be removed in 24 hours, but appropriate fluid substitution must be provided. The main limitation of CAVH is hemodynamic instability that is frequently observed in patients with crush syndrome as well as a high risk of complications connected with the necessity of cannulation of one of big arterial vessels. Possible complications include: haemorrhage, haematoma, thrombosis of artery affected by atheromatosis, formation of a hole in a vessel after a long-term cannula placement in its lumen, disconnection of a system [3,8].

Implementing continuous veno-venous hemofiltration (CVVH) requires only intravenous access and in this procedure double-lumen cannula is recommended. In all veno-venous methods blood flow is generated with a simple, one-head roller pump, which works independently of patient's systolic arterial pressure. CVVH can be successfully applied in patients with hemodynamic instability (very common in crush syndrome), whose systolic arterial pressure is lower than 70 mmHg [3,11]. In spite of the fact that continuous veno-venous hemofiltration increases slightly needs for technical equipment and one-head roller pump in filtration system brings about the necessity of automatic supervision of blood pressure and air bubbles in blood, CVVH embodies all major advantages of spontaneous arteriovenous hemofiltration and frequently it replaces this hemofiltration in everyday practice of intensive care units. During hemofiltration it is possible to filter 25-50 litres within 24-hour period [11,16].

Continuous veno-venous hemodialysis (CVVHD) is a technique similar to veno-venous hemofiltration, but dialysis fluid passes slowly through a dialyzer and in a direction opposite to the flow of blood. It is so-called counter-current multiplication, which increases diffusion efficiency and enables filtration of 30–50 litres per day. That is why hemodialysis is recommended for patients with increased catabolism [11,16].

Hemodialysis a good method for removing fluids and electrolytes as well as low-molecular solutions (< 300 Daltons), therefore, its use is not appropriate in crush syndrome treatment [11,16].

Regardless of the type of used hemofiltration method, continuous therapy enables permanent control of fluid balance and water-electrolyte balance, maintaining hemodynamic stability and preventing fluctuations of intracranial pressure. Its additional advantages are high biocompatibility and minimal infection risk [11]. Another positive aspect of this therapy is a possibility of precise compensation of water-electrolyte and acid-basic balance disturbances. Continuous renal replacement therapy (CRRT) apart from adequate supply and fluid removal enables control of protein metabolism products, and what follows, implementing nutrition with appropriate protein contents because demand for proteins in acute renal failure is 1–2 g/kg/24 hours. A proper diet for patients with rhabdomyolysis is a key element of treatment and should be implemented as early as possible. Enteral nutrition should be administered always when patient's general condition is satisfactory. Daily calorie demand is 30–35 kcal/kg/24 hours and is connected with lipid and carbohydrates supplementation. Vitamins and microelements should be provided in doses covering daily requirements [3,17].

Fluids and medicines administered to patient can also undergo filtration. Removing drugs during dialysis or continuous hemofiltration depends on their pharmacological characteristics, such as pharmacokinetics, molecular mass, renal clearance, degree of plasma protein binding. Some drugs, e.g. imipenem, are a combination of two ingredients with different pharmacokinetics and clearance [13]. Some drugs' ability to permeate hemofilter membrane is characterised by sieving coefficient (Sc), which is calculated mathematically as the ratio of drug concentration in ultrafiltrate to its concentration in plasma. This coefficient fluctuates between 0 (for substances not undergoing filtration) to 1 (for drugs passing freely through membrane pores) [11,13,17]. Dealing with such a situation requires the

knowledge of filtration degree of drugs administered to patient and proper modification of their doses. Catecholamines should be titrated till therapeutic effects are observed. Standard doses of amphotericin B, ceftriakson and erytromycine should be used. Aminoglycosides must be administered in unaltered doses, increasing intervals between them up to 36 hours and kotrimoksazol – every 18 hours. The following antibiotics are to be administered every 8 hours in a dose of 0,5 g: imipenem, meropenem, metronidazole, amoxicillin and ampicylin. Doses of the following drugs must be modified thoroughly: cefotaxime and ceftazidime (1 g every 8-12 hours), vancomycin (1 g every 24 hours), piperacillin (3–6 g every 6 hours), ticarcillin (1–2 g every 8 hours), ciprofloxacin (0,2 g every 12 hours), fluconazole (0,2 g every 24 hours), acyclovir (0,0035 g/kg of body weight/24 hours) and ganciclovir (0,005 g/kg of body weight/24 hours). When administration of drugs with a low therapeutic index (digoxin, aminoglycosides, vancomycin) is combined with continuous hemofiltration techniques, their concentration in blood must be monitored. Doses mentioned above are approximate ones and they are to serve as an indicator of their therapeutic range. These doses apply to continuous veno-venous hemofiltration (CVVH) at the ultrafiltration level of 2 l/per hour [11,18,19].

Blood flowing through drain system of extracorporeal circulation activates coagulation cascade and evokes clot formation on hemofilter. In order to prevent this process heparin is often administered. It increases the risk of complications i.e. bleeding. In order to help majority of patients small doses of heparin (< 10 IU/kg/per hour) are sufficient. The method is efficient and simple. Heparin activity can be reversed by applying protamine sulphate. However, in some cases it is necessary to administer big doses, sometimes even full heparinization is required especially when aggravating illnesses such as pulmonary embolism or myocardial infarction are observed [11].

Low-molecule heparin shows also high efficiency, but its administration is much more expensive, and what is more important, difficult to reverse because it accumulates in failing kidneys [2,11].

Local anticoagulation, when citrates are added to dialysis system, is effective and decreases risk of complications to minimum. This procedure, however, requires high pharmacological supervision, special dialysis fluid and it should be conducted in intensive care units [11].

Renal replacement techniques in acute renal failure are a relatively safe and well-tolerated treatment. However, some complications can always occur and they deserve special attention. They result from blood vessel cannulation and reactions of organism with multiorgan failures to homeostasis changes that occur during treatment as well as from the mechanism of renal replacement techniques or its failures [2,11,16].

Bleeding episodes in patients undergoing renal replacement therapy are quite common. They appear most often in the form of extrameningeal angioma and arachnoid, bleeding into pleural cavity, retroperitoneal space, eye anterior chamber and pericardial sac. Bleeding usually results from coagulation disorders caused by heparanization [11].

Hypotension is the most frequent complication. It can result from circulatory failure in e.g. bleeding, sepsis, myocardial infarction, cardiac arrhythmia and also can be caused by systemic reaction to component of dialysis system or by intolerance of semipermeable membrane [2,11].

Air embolism, although less frequent in modern equipment, can still be fatal. The most common way of air entry into the body is open arterial cannula, leaking arterial drainage system or central cannula left unclosed. The symptoms of this complication depend on air volume in vascular system and on body position. In patients in sitting position embolic material passes to the brain and causes ischemic stroke, whereas in lying patients it is located in right ventricle and leads to pulmonary embolism. Presence of air in dialysis system and suspicion of embolism requires immediate closure of venous line, placing patient in Trendelenburg position and commencing ventilation with 100% oxygen [11].

Implementing renal replacement therapy is often connected with hypoxemia. Its causes are hypoventilation, resulting from carbon dioxide elimination during dialysis, or from using sodium bicarbonate in urine alkalization and treatment of metabolic acidosis. It may also be caused by respiratory failures during bronchopulmonary sequestration with leucocytes as a result of systemic reaction to incompatible dialysis membrane [11].

Hyperthermia is quite often observed in renal replacement therapy and can be a symptom of infection or reaction to dialysis. When it occurs within one hour after implementing therapy it is usually a reaction

to pyrogenic substances that were found in dialysis system. Treatment is based on eliminating causes and administering antipyretic dugs. Sometimes heating dialysis fluid to temperature above 51°C can trigger a strong reaction i.e. acute hemolysis and hyperkaliemia. Under these circumstances it is obligatory to stop dialysis and not to let blood from the system come back into patient's body [11,19].

Two syndromes are characteristic for renal replacement therapy: first-use syndrome and dialysis disequilibrium syndrome. The first one is observed shortly after a change of dialyzer. It manifests by itching, pain, hypoxia and hypotension. It is induced by cellulosic semipermeable membranes, but can be prevented by using synthetic membranes of higher biocompatibility. Acute anaphylaxis, accompanied by bronchospasm and dilatation of vascular bed can be an allergic reaction to ethylene oxide that is used during sterilization of dialysis equipment [11].

Dialysis disequilibrium syndrome is a central nervous system disorder that is characterised by a range of neurological symptoms: headache, sight disorder, muscle twitching, nausea and vomiting as well as hypotension and cardiac arrhythmia. The most severe forms of this syndrome include: convulsions, loss of consciousness, coma and death. The cause of this complication is probably a sudden pH disturbance of cerebrospinal fluid which leads to cerebral oedema. Factors inducing dialysis disequilibrium syndrome are: acute metabolic acidosis, old age and co-occurence of central nervous system disorders. It can be prevented by avoiding rapid flux dialysis in the initial stage of therapy and administering osmotically active drugs such as mannitol and administering phenytoine to patients with acute renal failure who are susceptible to this complication. Sudden death during dialysis is fortunately a very rare complication of renal replacement therapy. It can be a result of: brain invagination caused by fluctuations of intracranial pressure, air embolism, acute pericardial tamponade, cardiac arrhythmia caused by dyselectrolytemy, haemorrhage (idiopathic and iatrogenic) or disconnection of dialysis system [11].

Prognosis in crush syndrome is always very grave. It depends on the length of time, extent and force of trauma, i.e. the degree of tissular ischemia and on the course of acute renal failure that occurs always in this condition. Clinical course of crush syndrome depends also to a great extent on patient's age, pre-accidental burden of pathologic changes, including mainly: kidneys, liver, lungs and cardiac muscle. When the development of some acute illnesses is predicted it is necessary to implement activities preventing acute renal failure, acute circulatory and respiratory failure and sepsis, all of which are the main direct causes of death in crush syndrome.

Crush syndrome treatment is a very dynamic process that requires multidimensional procedures. Implementing renal replacement therapy in the form of continuous veno-venous hemofiltration enables to prevent it successfully and treat acute renal failure which is a consequence of rhabdomyolysis.

In spite of continuous development of medicine, threats in the modern world still increase the risk of incidents with a high number of victims, such as catastrophes, wars, natural disasters and an increasing number of transportation accidents. Crush syndrome is then a real, frequent problem, therefore, doctors, paramedics and other medical staff members show nowadays a growing interest in this issue [2,5,8,20].

Conclusions

Recognition of crush syndrome requires:

1. Urgent implementation of anti-shock treatment in intensive care units.
2. Appropriate laboratory diagnosis (including e.g. determination of myoglobin concentration, electrolytes and muscle enzymes) and microbiological diagnosis.
3. Implementing treatment aiming at:
   - Adequate hydration.
   - Inducing osmotic dieresis.
   - Urine alkalization.
   - Considering commencement of continuous veno-venous hemofiltration (CVVH).
   - Providing best care, physiotherapy and rehabilitation.

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