TOPICAL REVIEW

Ischaemic-reperfusion damage of tissue and critical limb ischaemia

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Abstract

Recently, the quality of the critical limb ischaemia therapy (CLI) has evidently increased due to the development of the surgical techniques, material and endovascular methods. Most vascular surgeons, in their effort to help patients, advocate an active approach to re-vascularisation also in those patients who in the past had to undergo primary amputation.

The fact that the best results of re-vascularisation are referred from large specialised centres cannot be contested. One of the expected causes of re-vascularisation failure (local or complex) is also ischaemic-reperfusion damage (IRD) of the tissue (Fig. 3, Ref. 27).

Key words: ischaemia-reperfusion, no-reflow phenomenon, compartment syndrome, myonephrophatic metabolic syndrome.

Vascular diseases belong among the most frequent causes of mortality and morbidity of our inhabitants. Coming out of assumption of the register of vascular surgery for 2004, the incidence of critical limb ischaemia in Slovakia was 5,000 newly diagnosed patients. Twenty-five % of patients with CLI had to undergo amputation, which represents 1,200 amputations of lower limbs. This problem is highly topical, especially in the Slovak republic, where mortality due to cardiovascular diseases increased from 54 to 56 %, while critical limb ischaemia (CLI) in the population over 65 years has had dangerously increasing tendency, and the fact that 50 % of patients with CLI will die during 5 years since making diagnosis is alarming (Šefránek , 2000).

Ischaemia

Ischaemic-reperfusion damage of the tissue (IRD) in the patients with ischaemia of lower limbs (LL) is still actual problem that has to be solved relatively often. Most of the present knowledge about IRD has been connected with acute limb ischaemia, but in reality, IRD arises, in a lesser or greater degree, at every re-vascularisation. Ischaemia itself causes morphological and patho-physiological changes leading to subsequent clinical status that manifests according to the fact which tissue or organ is affected. After recovery of the blood circulation there is a clinical status with local and complex consequences. Regarding the fact that these two given pathological relationships are closely linked, it is suitable to use for them the term acute ischaemic-reperfusion syndrome (Forbes et al, 1995; Hickey et al, 1995).

Within the state of ischaemia – devascularisation, the clinical picture is characterised by four typical symptoms:

– very pronouced pain;
– pronounced ischaemia of affected tissues;
– limb and muscular rigidity;
– extensive limb oedema.

The degree of damage at ischaemia depends on the capacity of collateral bed, time factor and kind of tissue. Concerning the energy metabolism, there is a change in obtaining energy from the oxidative phosphorylation to the anaerobic glycolysis in mitochondria, which leads to depletion of the ATP (adenosine-triphosphate) and creatininephosphate depots. From the clinical point of view, it is of great importance that changes in the energy metabolism are more pronounced at working muscle in comparison with resting one. The amount of ATP originating from this process contains close on 19-times less energy.

Reactions of the citrate cycle are attacked, whereas pyrurvate reduces to lactate. Accumulation of lactate leads to a decrease in pH and to metabolic acidosis.

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A slighter degree of acidosis in the ischaemic tissue has been known long ago to have a protective effect. A slight acidosis has reserving effect on the depletion of ATP depots. It is owing to preserving the functionality of the membrane transport systems, which at the values close to 7 retain sufficient trans-membrane proton gradient (Firt et al., 1991; Pecháň et al., 1999).

Due to reduction in the formation and depots of ATP, the integrity and function of cellular membranes is insufficient. The exogenous supply of ATP with phosphoenolpyruvate has been proved experimentally to be able to inhibit formation of a superoxidised anion (Lacková et al., 1996; Lierman et al., 1997). In the state of deepened metabolic acidosis and transport system disorder there is a massive dislodgement of potassium into the cellular compartment as an exchange for sodium cations.

Calcium, accumulating in the cell cytosol, is released from the sarcoplasmatic reticulum. Excessive accumulation of calcium in the intracellular compartment leads to activation of calcium-dependent proteinases that under hypoxic conditions convert xanthine dehydrogenase to xanthine oxidase. At re-perfusion (under aerobic conditions) there is a massive formation of free oxygen radicals at conversion of hypoxanthine (product of energy ATP degradation) to uric acid (Vájó, 1996; Mondek et al., 2004), (Fig. 1).

Free oxygen radicals (FOR), forming in an increased degree in mitochondria, are inactivated by the antioxidative system of the cell, which is formed, above all, by superoxididismutase, glutathione peroxidase, catalase, and the group of SH substances, especially reduced glutathione, what has a key significance for cell survival (Adembri et al., 1994; Pecháň et al., 1995; Petrášová et al., 1998).

**Re-perfusion**

The specific cause of the origin of the revascularisation syndrome is not known. Its development through the time factor could not be explained. It could also arise after very short persisting of ischaemia, some other time it is not observed after ischaemia lasting for a longer time. The explanation could be in the anoxia that arterial occlusions do not have to be complete, and a certain part of circulation could be ensured by collaterals that are developed, especially in the patients with atherosclerosis.

Larcan et al. (1973) reported that for the development of the revascularisation syndrome interaction of more circumstances is needed:

1. Ischaemia has to be on the bulkier muscular groups – therefore in the region of lower limbs this syndrome is much more clearer;
2. Ischaemia has to be complete. Where the collateral circulation is good, the revascularisation syndrome does not appear.

At postischaemic reperfusion the recovery of oxygen supply as well as oxidising phosphorylation occur in cellular organelles. The rate of recovery of the energy metabolism does not correspond to the rate of recovery of the function of muscular tissue. The rate of the contractility restoration is slower than the rate of recovery of the oxidising phosphorylation. Reversibility of functional changes is dependent on the threshold value, decrease in the ATP depots and creatinephosphate for a given muscle.

At anti-ischaemic reperfusion, recovery of the oxygen supply and oxidising phosphorylation occurs in the cellular organelles – so called the oxygen paradox, i.e. for a given contractile ability of the muscular tissue the oxygen consumption is excessively high, which forms suitable conditions for formation of reactive forms of oxygen that only deepen impairment of biomembranes. The changes occurring at this are local and systematic (Pecháň et al., 1999; Veith et al., 2000) (Fig. 2).

Local changes: peroxidation of lipids, denaturation of proteins, membrane impairment, permeability disorder, cellular oedema, interstitial oedema, activation of leucocytes, aggregation of blood elements, microcirculation failure, and origin of
Reperfusion

ATP

↓

ADP

↓

AMP

IMP Adenosine

Inosine

Xanthine dehydrogenase

↓

Xanthine oxidase

O$_2^-$ H$_2$O$_2$ OH$^-$

uric acid

O$_2$

Fig. 2. Formation of free oxygen radicals during reperfusion (according to Schoenberg and Paes, 1989).

“no-reflow” phenomenon, and so-called “compartment syndrome”.

“No-reflow syndrome” is the state, when the endothelium oedema, permeability disorder, and microprecipitation of thrombocytes occur in the metabolically active part of vascular bed (capillaries).

Compartment syndrome (CS) is defined by increasing of the tissue pressure in the closed fascial space with subsequent disorder of the blood circulation, and origination of ischaemic structures inside this space. Since the first clinical description of CS passed more than 100 years. 80 years ago Jepson described in the experiment the importance of early decompression of the fascial space as prevention of ischaemia. CS originates after revascularisation of the ischaemic tissue most frequently due to arterial embolism, or trauma. The incidence of CS in these states is 10%, in combined traumas (artery, bone, muscle) 30%. The principle of the origin is so called capillary leak due to ischaemia, and subsequently reperfusion, which is further potentiated by arising of free oxygen radicals and inflammatory mediators. The pressure limit inside the compartment at which CS originates is highly variable and defined by the diastolic pressure. However, it is different at the states of hypotension, or vasoconstrictions. The length of ischaemia (nerves <2 hrs, muscles <6 hrs) is very important for the limb fate. Pulsations on the peripheral arteries are not decisive for CS diagnosis. The development of painfullness, tension and rigidity of the appropriate space is determining. The disorders of sensitivity and mobility are the sign of the progress and often irreversibility of CS. In unconscious patients besides the clinical symptoms of CS a suitable addition is pressure measurement inside the compartment that must not exceed 40 mmHg, or to be higher than 30 mmHg for 4 hrs. Prevention of the CS arising appears to be in preoperative sufficient hydration of a patient with application of scavengers of free oxygen radicals (mannitol, selenium, zinc, vitamins), and in long-lasting limb ischaemias performing fasciotomy at the same time with reconstruction. Fibulocetomy is not indicated at sufficient fasciotomy. At present, the CS occurrence is not special at continuously increasing number of polytraumas. There is, however, specialness, when due to untreated CS after successful arterial surgery high amputation is necessary (Trčška, 2002).

Systematic changes: represent acidosis, hypercalemia, myoglobinuria, renal failure, cardiac arrhythmia, haemolysis, decrease in blood pressure, microembolisation, and ARDS.

It is a case of changes as metabolic as haemodynamic. After recovery of circulation in the ischaemised musculature a dislodgement of degraded product of the muscular tissue and anaerobic metabolites. Subsequently in venous blood of the re-perfuse limb, but also in the complex circulation the level of lactic acid and calcium increases and at the same time pH rapidly decreases and pCO$_2$ increases. Pronounced hypercalemia could lead to cardiac standstill, sometimes immediately after revascularisation or later during anuria. In the first hours of the revascularisation stage high levels of creatinephosphokinase (CPK), lactatehydrogenase (LDH), glutaminolatransaminase (GO) are found in venous blood (Forbes et al., 1995; Čertik, 2003).

The haemodynamic changes, in the sense of hypovolaemic shock, are caused by the plasma loss into tissues. This results in haemoconcentration, vasoconstriction, centralisation of circulation and insufficient congestion of kidneys and liver. Myoglobinurina along with insufficient renal perfusion and under conditions of metabolic acidosis can lead to acute renal failure based
upon tubular necrosis. Muscular tissue undergoes changes – rhabdomyolysis at which the musculature is pale, oedematous. After successful revascularisation interstitial bleeding, fibrin deposition, and marked oedema of muscular fibres are observed. Coming out of clinical-pathological and metabolic view for a set of symptoms related with massive ischaemia and revascularisation the term “moynehphrophathic metabolic syndrome” is used (Dawson et al., 2001; Puchmayer, 2003) (Fig. 3).

**Conclusion**

Ischaemic-reperfusion damage (IRD) of the tissue in the patients with ischaemia of lower limbs is still the object of scientific interest. A degree of damage is, in lesser or greater degree, expressed individually in every patient, regardless whether it is acute or chronic ischaemia. The difference is only in the extent of damage and clinical manifestation. A sudden occlusion or decrease in blood supply to tissues or organs will cause ischaemia that could be of various degrees.

Up to now there have not been any reliable predictors on the basis of which it could be predicted preoperatively the arising and extent of IRD. From the clinical point of view, it is considered to be very important to control the IRD origin, premedicate patients with antioxidatively acting substances and to treat IRD immediately after initial suspicion in order to prevent the origin of the Compartment syndrome or SIRS (systemic inflammatory response syndrome) and subsequently the multi-organ failure.

The patho-physiological mechanisms of IRD is complicated, and in some cases not fully clarified. One of the basic expected causes of the IRD origin is premature activation of PMN leucocytes by the contact with ischaemia-damaged tissue in the reperfusion phase. The goal of activated PMN leucocytes is demarcation and destruction of the impaired tissue. A release of vaso-active substances (histamine, serotonin), increase in capillary permeability, local oedema and formation of free oxygen radicals occur. In case that the given local inflammatory reaction continues, there is a development of systemic inflammatory response (SIRS) that could lead to the syndrome of multi-organ failure and the patient death (Summers et al., 1995; Šramková, 2000; Mondeč et al., 2004).

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**Fig. 3. Degrees of cellular damage during reperfusion (according to Paetz and Allenberg, 1992).**

### Damage at ischaemia

- Reversible
  - Potentially reversible
    - uncontrolled
  - Irreversible

### Result of reperfusion

- Restitutio ad integrum
  - modified reperfusion
  - Cellular death


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