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Review

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Surgeons are confronted with ischemia-reperfusion (IR) injury more often than they anticipate. Hypoperfusion associated with hypotension and hypovolemia is probably the most common cause of non-occlusive ischemia. When this patient in hypovolemic shock is recussicated and tissue perfusion restored, the treating physician or surgeon is faced with the reperfusion injury (1). Organ transplantation is another example where the transplanted organ is reperfused after a period of ischemia. The surgeon is faced with IR injury when an incarcerated hernia is reduced or a volvulus of sigmoid colon is detortioned. Occlusion of the portal triad with the Pringle maneuver during liver surgery renders the liver ischemic and reperfusion injury begins when the occluding clamp is released. Surgeons, for long years, had difficulty in understanding the cause of renal failure and death after an apparently successful embolectomy from the femoral artery.

Although the human body has its own defense system, understanding the pathophysiology of IR injury is essential for the surgeon in preventing and/or treating the reperfusion injury in common clinical practice as there are times when the organism fails. In this review, after a brief description of IR injury and natural defense systems, IR injury associated with organ transplantation, mesenteric IR injury, and the role of reactive oxygen metabolites (ROM) in tumorigenesis will be covered.

Ischemia-Reperfusion Injury

Ischemia of an organ or system results in varying degrees of tissue destruction depending on the duration and extent of occluded arterial blood flow. The damage induced by ischemia also depends on the tissue characteristics as some organs can withstand ischemia better than others (2). During ischemia the cell is deprived of the energy needed to maintain ionic gradients and homeostasis. Following ischemia, reperfusion is mandatory if the tissue in question is to survive. However, it has been clearly shown that reperfusion injury exceeds tissue destruction caused by ischemia alone (3,4). This injury is not only local but may have systemic consequences sometimes extending to multiorgan failure (5-7). Parks and Granger have demonstrated that, four hours of intestinal ischemia causes less damage than three hours of ischemia followed by one hour of reperfusion (8). Reperfusion injury is mediated by the interaction of ROM, endothelium and neutrophils. Xanthine oxidase metabolism, activated neutrophils, catecholamine oxidation, endothelial cells, and prostaglandins can generate ROM (3,9,10). In IR injury vascular endothelium also plays a pivotal role (11). The vascular endothelium, besides being a semipermeable membrane lining the lumen of the vessel, can be considered as a very active organ having important metabolic and endocrine functions (12). The damaged vascular endothelium can produce ROM and at the same time, the release of many substances can be affected. Arachidonic acid metabolites, nitric oxide (NO), endothelins (ET), complement activation, cytokines, and adhesion molecules all contribute to IR injury. In maintaining the vascular tonus during IR injury, NO and ET-1 control each other (13) and this relationship can be affected by agents which can act as ROM scavengers and/or angiotensin converting enzyme inhibition (14,15). Neutrophils are held responsible for both local and systemic injury and it has been shown that depletion of circulating neutrophils effectively prevents permeability and edema formation (16,17) (Table 1).

Several endogenous mechanisms exist to overcome IR injury and a number of drugs have also been found to be protective (18,19) (Table 2).

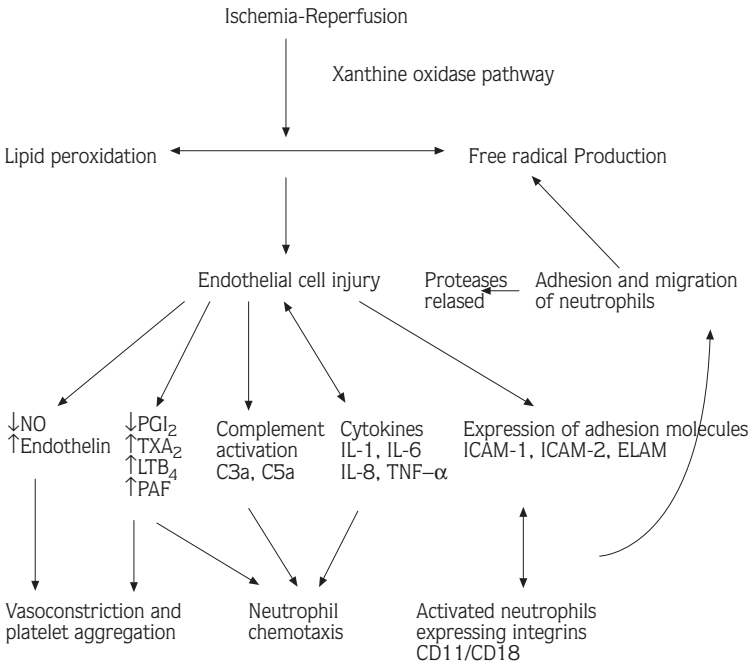

Table 1. Ischemia-reperfusion injury. NO, nitric oxide; PGI_2 prostacyclin; TXA_2, thromboxane A_2; LTB_4, leukotriene B_4; PAF, platelet activating factor; IL, interleukin; TNF, tumor necrosis factor; ICAM, intercellular adhesion molecule; ELAM, endothelial leukocyte adhesion molecule.

Table 2. Endogenous defence mechanism against ischemia reperfusion injury

A) Free radical scavengers
Catalase
Superoxide dismutase
Histidine
B) Antioxidants
Vitamin A (α-tocopherol)
Vitamin C
C) Neutrophil inhibitors
Adenosine
Transforming growth factor ß

Organ Transplantation

Organ transplantation (tx) offers the best chance of studying clinical and experimental ischemia-reperfusion (IR) injury. However, most often, immunological aspects of tx accompanies IR injury. When an organ is retrieved from the body of the donor, ischemia begins and when the vascular anastomoses are completed and organ revascularized, reperfusion injury begins. Unlike many other clinical IR injuries, the time of ischemia and reperfusion is known and therefore appropriate interventions can be done at any period of IR injury.

Reperfusion of an allograft creates an acutely inflamed organ caused by ROM (20), cytokines (21,22), and adhesion molecules (23,24). Studies have revealed that leukocyte-endothelium interactions and extent of tissue injury depend on several factors including duration of cold ischemia (24) and the type of preservation solution (25). Prostacyclin was effective in maintaining the liver glycogen content after pig liver tx (26) and this property of prostacyclin is at least partly due to its cytoprotective effect in IR injury (27,28) Adhesion molecules have been shown to be very important in the early and late events after tx. Early injury by adhesion molecules are probably mediated by ROM as radical scavengers effectively diminish tissue injury (23,24). Endothelin is also an important mediator taking place in early events in renal tx as levels increase after tx and endothelin receptor blockers attenuate tissue injury (20).

In recent years, it has been proposed that ROM mediated IR injury, in addition to post ischemic changes, also triggers acute and chronic rejection (29). There is also increasing evidence that adhesion molecules are involved in the process of rejection (30). In the Munich rh-SOD trial it was demonstrated that long term survival of cadaveric renal allografts was superior in those patients who had received radical scavenger recombinant superoxide dismutase before reperfusion of the graft when compared with patients receiving placebo (31). Land and Messmer hypothesize that a primary non-specific and a secondary specific injury take place after tx and these events begin allograft ar-

teriosclerosis which is the major component of chronic organ rejection (29). The underlying mechanism for both conditions is proposed to be endothelial injury by ROM leading to cytokine and adhesion molecule induced vessel wall remodeling.

Mesenteric Ischemia-Reperfusion Injury

Mesenteric vascular bed is probably the best area to study IR injury. Conversion of xanthine oxidase to xanthine dehydrogenase takes only 10 seconds in the intestinal tissue. Xanthine oxidase is the major source of ROM production in IR injury. The time of conversion has been shown to be 8 min. in cardiac muscle and 30 min. in liver, spleen, kidney, and lung (5,32). This fact can also help to explain the different resistance of organs to IR injury. The mesenteric circulation is also important as the gut receives 20 % of the resting and 35% of postprandial cardiac output.

Non occlusive mesenteric ischemia encountered quite often in intensive care units, is the most common clinical mesenteric problem followed by reperfusion. In most other instances, resections are carried out for non-viable intestine where ischemia is not followed by reperfusion. Except its speed and intensity, pathophysiology of mesenteric IR injury is not much different from other organs. While some of the arachidonic acid metabolites such as leukotrienes and thromboxane A2 increase tissue destruction (33,34), prostacyclin is protective (35). IR injury is mediated by many cytokines and in recent years ET-1 has been shown to be one of them. ET-1 is very potent vasoconstrictor and its release is at least partly activated by ROM (36), unrelated to calcium influx (37) and probably mediated by PGE2 (38). However increased ET-1 by acting on different receptors may cause vasodilation and thus diminish IR injury (35,39,40). In mesenteric IR injury a delicate balance was also found between ET-1 and nitric oxide (13). These studies demonstrate the complex mechanism of IR injury where many factors interact. However, understanding this interesting cascade will help to overcome IR injury and at the same time many pathologies encountered in daily clinical life may be resolved.

Free Radicals and Carcinogenesis

Interest in the involvement of free radicals in carcinogenesis has increased significantly in recent years (41,42). This is natural since free radicals are formed in biological systems and contribute significantly to physiological and pathological processes (43). The intracellular concentration of ROM is increased in prooxidant states, because cells either overproduce these reactive substances or are deficient in their ability to destroy them (42,43). Prooxidant states vary, depending on the type of target cell and on the induction mechanism, and can result in cell damage through readily oxidizable target molecules. Major reactions are initiation of lipid peroxidation and other autooxidation chain processes, addition of hydroxyl radicals and singlet oxygen to double bonds, hydrogen abstraction, and oxidation of sulfhydril, thioether and amino functions (43). Among the biological consequences are mutations, sister chromatid changes, chromosomal aberrations, cytotoxicity, carcinogenesis, and cellular degeneration related to aging. Free radicals appear to play a role mostly in the promotion phase of carcinogenesis, during which gene expression of initiated cells is modulated by affecting genes that regulate cell differentiation and growth (44,45). Chemiluminescenece studies have revealed that superoxide formation increases in adenocarcinoma of the colon and there appears to be a relationship between the grade of the tumor and the amount of superoxide formation (Aktan AÖ,Yalçın AS unpublished data).

Antioxidants protect against deleterious effects of ROM via inhibition of radical formation, decomposition of peroxides or inactivation of metals (46). Antioxidants are generally not mutagenic as evaluated in several mutagenesis assay systems and they even inhibit the mutagenic activity of some mutagens. Moreover, they inhibit chemical carcinogenesis when they are given prior to and/or simultaneously with certain carcinogens (47,48). There is some evidence of a relationship between a decrease in the incidence of and mortality from cancer of certain organs and consumption of antioxidants. The incidence of certain cancers in population is inversely related to the amount of selenium in the environment. There is also an inverse association of dietary intake of beta-carotene or vitamin C and cancer incidence. Serum vitamin E and beta-carotene and the risk of all histologic types of cancer and squamous cell carcinoma of the lung appear to be inversely correlated (47). Diet has long been hypothesized to play a an important role in the etiology of cancer. It was suggested that as much as 35% of all malignancies might be related to dietary practices. The antioxidants beta-carotene, vitamin E and vitamin C are among the constituents of diet proposed to play a preventive role in cancer. The possible benefits of antioxidant vitamins on cancer depends on their ability to trap free radicals and/or deactivate ROM. Epidemiological studies have raised the possibility that geographic differences in cancer incidence

might be explained by regional variations in intake of antioxidant vitamins, and analytic epidemiological studies among individuals have demonstrated inverse associations between dietary intake or blood levels of antioxidants and risks of cancer (48). Thus, currently available data are compatible with the possibility that antioxidant vitamins may decrease risks of cancer.

It is evident that surgeons are confronted with ROM in everyday life and understanding this complex mechanism of superoxide formation will help the surgeon to overcome certain still unresolved clinical problems.

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