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Ischemia Reperfusion Injury in Kidney Transplantation

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1. Introduction

Ischemia and reperfusion have been a natural step during kidney transplantation. Impairment of blood flow starts with brain death due to severe hemodynamic disturbances in cadaveric donor. Clamping of renal artery causes an absolute ischemia during harvesting operation. Cold ischemia during allograft kidney storage may also cause additional ischemic damages (Southard et al. 1985; Ploeg et al. 1988; Dong & Tilney 2001). On the other hand, allograft kidney transplantation from living related donor is also subjected to warm ischemia beginning from arterial clamping. Following the blood flow reconstruction in kidney transplantation, the final stage of injury occurs during reperfusion –so called reperfusion injury. Ischemia reperfusion injury is actually an immediate nonspecific inflammatory response (Koo & Fuggle 2000). In this response, endothelium is activated by reactive oxygen species and inflammatory cytokines, then adhesion molecules like P-selectin and E-selectin are involved and induce the adherence of platelets to the epithelium. Leukocytes, initially neutrophils then monocytes and macrophages infiltrate into the affected tissue besides T lymphocytes (Koo & Fuggle 2002).

The pathophysiological changes associated with ischemia/reperfusion injury in renal transplantation are not yet well defined although it has been studied extensively (Koo et al 1998). However, it is well known that prolonged cold ischemia is associated with delayed graft function with elevated creatinine levels in addition to inferior graft survival on long term follow up (Homer-Vanniasinkam et al. 1997; Land 1999). Animal studies showed that the main mechanisms were related to leukocyte-endothelium interactions, reactive oxygen species, and the complement system (Kurokawa & Takagi 1999). Many interrelated pathways also control these fundamental biological systems. Free radicals appear to mediate tissue injury through lipid peroxidation and the activation of endothelial cells, resulting in functional and structural cell damage. Apoptosis and cell necrosis also take place as a result of injury. The disturbance of microcirculation in the graft besides mitochondria and some other cellular organelles are parts of these changes (Jassem et al. 2002). The main pathological changes are cellular death of affected tissue. Many other factors including the duration of ischemia dictate the magnitude of injury (Massberg et al. 1998; Land 1999; Gulec et al. 2006). The age and types of tissue are strongly correlated to the magnitude of damages in ischemia and reperfusion (Homer-Vanniasinkam et al. 1997; Torras et al 1999).

2. Mechanism of ischemia reperfusion injury

Many studies have been employed to explain the damage caused by ischemia reperfusion injury (Land 1999). Blood flow stops and substrates and energy are deprived of so that cellular homeostasis and ionic gradient can not be maintained anymore. This is a stressful state for the affected cells. In the beginning of ischemia, adenosine triphosphate is provided by glycolysis. However, glycogen stocks are limited and soon are emptied meanwhile waste products and toxic metabolites including lactate are accumulated. By changes in metabolism during ischemia, intracellular pH falls as a result of anaerobic glycolysis and the hydrolysis of adenosine triphosphate. It is surprising that, restoration of a normal pH during reperfusion in ischemic cells accelerates cell killing, a phenomenon called the 'pH paradox'. If ischemic cells are reperfused at acidotic pH or a rise in intracellular pH after reperfusion is inhibited, cell killing is abrogated. In contrast, the rise in intracellular pH during reperfusion provokes cell killing. Reperfusion exacerbates this damage by triggering an inflammatory reaction involving oxygen-free radicals, endothelial factors, and leukocytes (Figure 1). This triggering disrupts the microcirculation with attraction, activation, adhesion, and migration of neutrophils (Massberg & Messmer 1998). Actually, the target site of ischemia reperfusion injury is the vascular endothelium and the microcirculation of the graft.

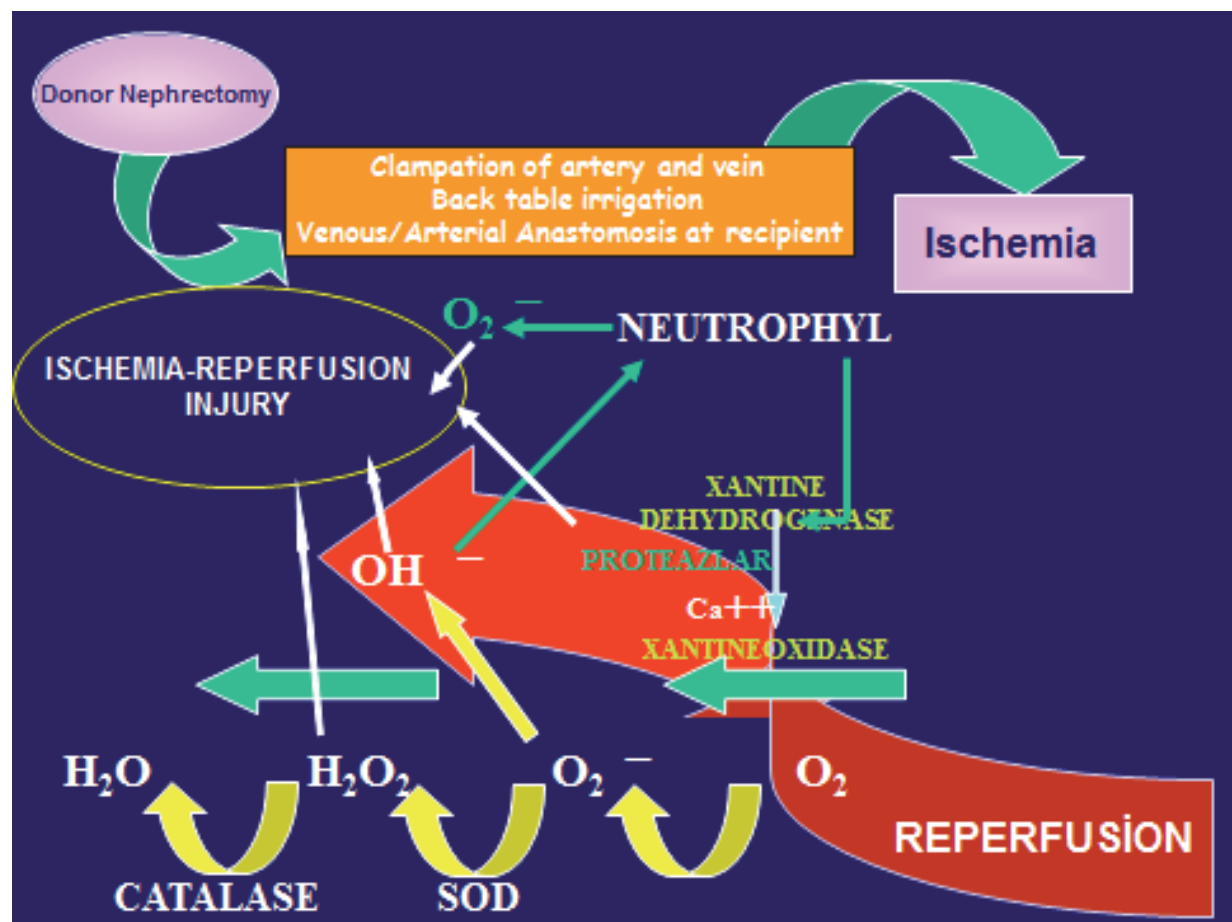


Fig. 1. The ischemia reperfusion injury

In order to understand mechanisms involved in ischemia reperfusion injury, initial and late phases should be evaluated. Activation of leucocytes and interactions between leucocytes and endothelium provoking inflammation take place at initial phase and release of reactive

oxygen species from different sources, activation of complements and triggering the innate immunity causing apoptosis and necrosis of the cells are late phase response following ischemia reperfusion injury. Chemotactic mediators during ischemia, activate leucocytes and enzymes like phospholipase A2 which converts cell membrane phospholipids into arachidonic acid, and lysozymes which are proteolytic digesting pathogens and necrotic cells (Figure 2). Arachidonic acid itself is a precursor for inflammatory mediators such as leukotrienes and prostaglandins. By way of lipoxygenase and cyclooxygenase pathways, metabolites of arachidonic acid but mainly the leukotrienes increase the vascular endothelial adhesion of leukocytes and increase the postcapillary permeability. On the other hand, when leukocytes bind to endothelium, adhesion molecules such as P selectin and L selectin besides intercellular adhesion molecule (ICAM) occur and make more leukocytes adhere to the site. It is sure that reperfusion will increase these interactions between leucocytes and epithelium. Actually, leucocytes release some chemotactic agents recruiting much more leucocytes in the area. Leucocytes also release lysozymes and produce reactive oxygen species which are essentials in ischemia reperfusion injury. It has been shown that activated neutrophils also release elastase, cathepsin G, heparanase, collagenase and hydrolytic enzymes that are likely to be directly cytotoxic to hepatocytes (Kang 2002).

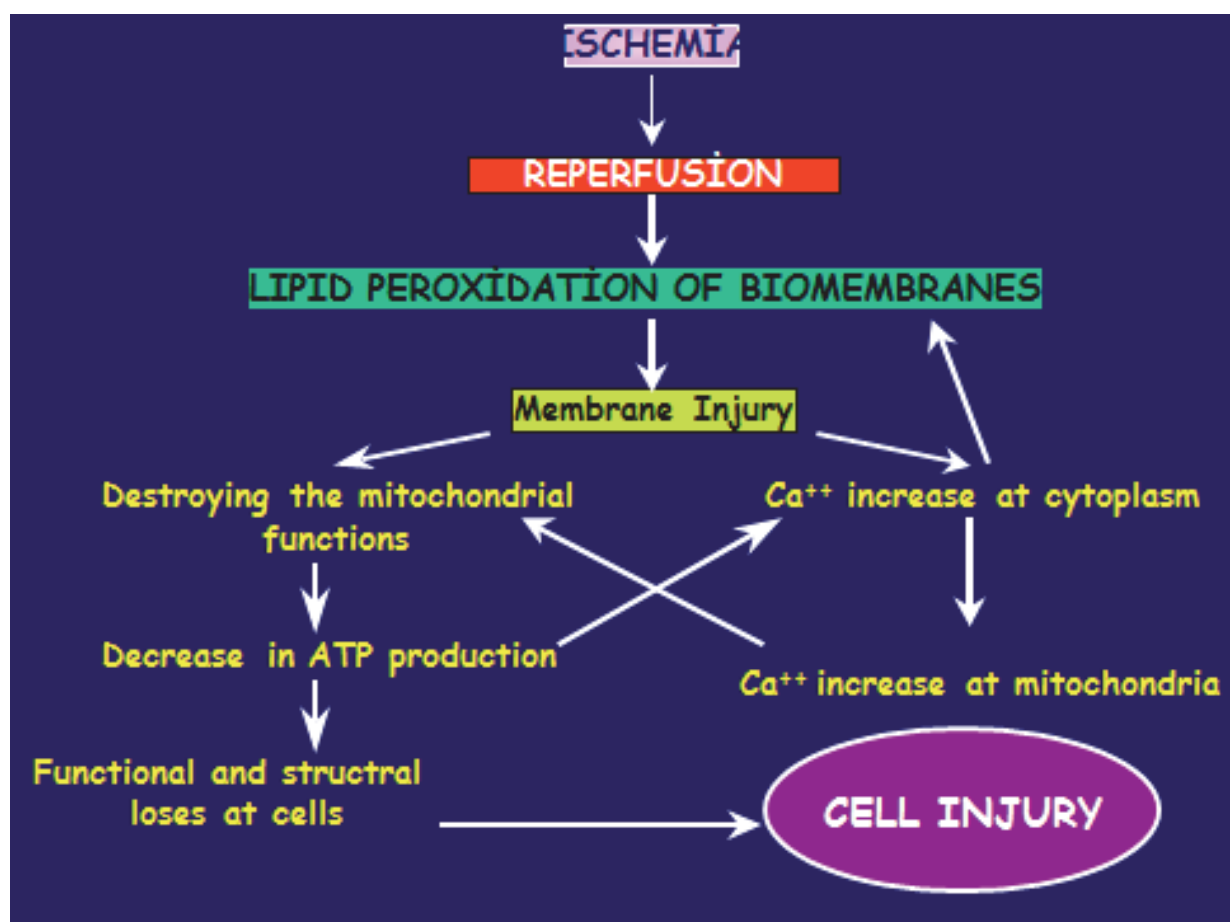


Fig. 2. Lipid peroxidation of biomembranes in ischemia reperfusion injury

Reactive oxygen species as highly unstable oxygen molecules with unpaired electrons are capable of oxidizing many biological molecules, such as proteins, lipids, and DNA. They

react with the cell membrane causing lipid peroxidation. Lipid peroxidation affects leucocytes and platelets so that further vasoconstriction and the diminished perfusion occur. The antioxidant activity of glutathione, superoxide dismutase, and catalase in the body control the concentrations of reactive oxygen species. Reactive oxygen species can be released by way of different ways in various tissues like through cytochrome P450 in lung or xanthine oxidase and cyclooxygenase in endothelium or nicotinamide adenine dinucleotide phosphate oxidase in leucocytes (Khalil et al. 2006). In animals with nicotinamide adenine dinucleotide phosphate oxidase deficiency, interestingly enough reperfusion injury is still observed (Hoffmeyer et al. 2000). It suggests that reactive oxygen species are solely not the only contributor to reperfusion injury.

The terminal complement complex and C5a are the complement activation products mainly involved in tissue injury by ischemia reperfusion (Ferraresso et al. 2000). As a part of nonspecific inflammatory response, the deposition of terminal complement components in reperfused tissue has been detected. In contrary, depletion of complements in animals reduces the extent of injury (Amsterdam et al. 1995). It suggests that complement is another key mediator of reperfusion injury by an alternative pathway. The formation of membrane-attack complexes is the end product that damages cells by creating pores in cell membranes. Complement activation releases chemotactic agent (C5a) and anaphylatoxins (C3a, C5a) that induce degranulation of mast cell and the release of chemical mediators like histamine etc. (Lazarus, et al. 2000). It has been suggested that antibody complexes may form during reperfusion injury (Austen et al. 2003). Studies by Williams et al. 1999 and Zhang et al. 2004 reported that immunoglobulin M plays a role in pathogenic injury with in situ evidence of immunoglobulin M and C3 and C4 complement deposition in damaged tissue.

The host innate immune system participates in inflammation. As the most potent antigen presenting cells, dendritic cells are also involved in this process. Epithelial and endothelial cells besides dendritic cells express so called toll like receptors which are activated by endogenous ligands. It has been clearly demonstrated that toll-like receptors signaling is involved in the immune recognition of kidney allografts (Obhrai & Goldstein 2006). Further investigation about innate immunity during transplantation will likely improve future therapeutic interventions in this area.

Ischemia reperfusion injury in organ transplantation is mediated as briefly described above by a complex mechanism ending with cell death by apoptosis and necrosis (Thomas et al. 2000). Although apoptosis is a unique and required mechanism to maintain normal physiology, growth, differentiation in a scheduled manner; cell damage in ischemia reperfusion injury can also induce apoptosis. (Thomas et al. 2000; Daemen et al. 2002)

3. Ischemia reperfusion injury during renal transplantation

A better understanding of the underlying mechanisms of ischemia reperfusion injury will help further improvements in graft survival. Post-transplant renal failure has been studied extensively. Almost 30 % of the delayed graft dysfunction following kidney transplantation is attributable to ischemia reperfusion injury (Jassem et al 2002). Apoptosis has been identified as a central mechanism in many aspects of organ and tissue transplantation, rejection, and immune tolerance (Thomas et al 2000). The classical effector enzymes of apoptosis, caspases are able to induce not only apoptosis but also inflammation following ischemia reperfusion injury in experimental models (Daemen et al. 2002). Indeed, ischemia reperfusion injury is one of the most important nonspecific and otherwise nonimmunologic

factor affecting both delayed graft function and late allograft dysfunction (Halloran et al. 1988; Womer et al. 2000).

The transplanted kidney may be susceptible to ischemia reperfusion injury at various stages of transplantation. Hemodynamic instability of cadaver donors may also cause repeated in situ warm ischemia attacks of kidneys. Warm ischemia may also be experienced during organ procurement. In situ cooling may be useful to minimize ischemia reperfusion injury during organ retrieval from a cadaveric donor (Koo et al 1998). However, organs from non-heart-beating donors are at risk of much longer periods of warm ischemia before cooling with iced perfusion solution at back table. Cold ischemia is another issue and allograft kidneys are exposed to some degree of cold ischemia during storage of kidneys from cadaveric donors. Although it is relatively short period of time, allograft kidney is subjected to cold ischemia during living related renal transplantation. When blood flow starts again, proinflammatory cytokines were released and innate immunity was activated by the reactive oxygen species mediated injury. This early innate immune response and the ischemic damage will initiate adaptive responses. Repair and regeneration process including cellular apoptosis, autophagy, and necrosis will take place. The final result is directly related to early and late function of the transplanted kidney.

Studies investigating the effects of ischemia reperfusion injury in clinical renal transplantation are limited. It is documented that the length of warm or cold ischemia is proportional to the incidence of delayed graft function in transplanted patients (Koo et al 1998, Mateo et al. 2002). Ischemia reperfusion injury in the allograft kidney provokes renal tubular apoptosis and inflammatory response that may stimulate alloimmunity against the graft (Lieberthal et al 1998; Daemen et al. 2002). Physiologic apoptosis does not provoke an immune response; moreover apoptotic cells may suppress inflammation. However, apoptosis following ischemia reperfusion injury instigate inflammation by way of activated caspases (Daemen et al. 2002). The most important of all, apoptosis requires adenosine triphosphate while necrosis can occur even in adenosine triphosphate depleted conditions.

Greene & Paller 1992, showed that rat proximal tubule epithelial cells produced reactive oxygen species in case of ischemia reperfusion. Glutathione and vitamin E as reactive oxygen species scavengers reduced the magnitude of injury. The role of polymorphonuclear leucocytes in ischemia reperfusion injury is upon revascularization. The adhesion molecules, ICAM-1 and VCAM-1 take place in mediating renal damage during reperfusion injury. Briscoe et al. 1992 showed that circulating ICAM-1 levels and ICAM-1 expression by proximal tubule cells have increased during acute rejection besides over expression of VCAM-1 at sites where T-cells accumulated.

Rainger et al. 1995, showed that reactive oxygen species induce adhesion molecule expression, resulting in activation and increased binding of neutrophils at human umbilical vein endothelial cells. In another experimental study by Shoskes et al. 1990, increased expression of adhesion molecules and neutrophil infiltration within hours of reperfusion, followed by mononuclear cell infiltration and up-regulation of major histocompatibility complex class II expression several days later have been shown following ischemia reperfusion injury of the kidney. These immunogenic changes triggered by the early nonspecific inflammatory events will play a major role in determining the quality of graft function in the long term.

Previous clinical studies on ischemia reperfusion have relied mainly on the measurement of malondialdehyde as a marker of lipid peroxidation, although elevated levels of malondialdehyde in plasma after reperfusion of the graft were not correlated with

subsequent graft function (Davenport et al. 1995). In the early era of transplantation, postperfusion state biopsy in order to evaluate hyperacute rejection was frequently obtained at an hour after revascularization. Neutrophil infiltration in the glomeruli was assessed as an indicator of hyperacute rejection of the allograft, although a direct correlation between neutrophil infiltrations and either hyperacute rejection or acute rejection episode was not established (Gaber et al. 1992). Due to modern pluripotent immunosuppressive agents and improvements in antibody screening and crossmatching, hyperacute rejection has been virtually eliminated. So that there is no need to obtain biopsy at postperfusion state. Gaber et al. 1992, stated that polymorphonuclear leukocytes detected in biopsies from cadaver renal allografts, were associated with long cold-storage times. They observed 4 hyperacute rejection cases of 57 allografts studied and concluded that it was not clear whether these polymorphonuclear leukocytes entered upon reperfusion or were already present within the donor kidney.

4. Remote organ effects of ischemia reperfusion injury following kidney transplantation

Transplantation of an ischemic organ can cause dysfunction in distant organs. Above mentioned various mediators are released into systemic circulation following ischemia reperfusion injury. These circulating mediators may be harmful at distant tissues and organs like native kidneys, lungs, liver and heart. Mediators like TxA_2 and LTB_4 may cause transient pulmonary hypertension by way of sequestration of leukocytes and increased capillary permeability (Anner et al. 1988). Inhibition of these eicosanoids greatly attenuates pulmonary injury. Electrolyte imbalance including potassium and hydrogen ions besides myoglobin released into the circulation following revascularisation of ischemic limbs can impair renal, cardiac and pulmonary functions. Similarly increased levels of $\text{TNF-}\alpha$, IL-1 , and IL-6 occur following hindlimb reperfusion and may influence PMN-mediated remote organ injury. Enhanced lung permeability is prevented by blocking these pathways (Seekamp et al. 1993).

Distant organ injury or multiple organ failure is the end point of remote effects of ischemia reperfusion injury. Pulmonary injury is a major component of all. Leucocyte sequestration in pulmonary tissue was prevented by inactivation of xanthine oxidase in a rat model of intestinal reperfusion (Terada et al. 1992, Poggetti et al. 1992). Both local and systemic tissue injury occurs following reperfusion of ischemic organ. It is now clear that the pathogenesis of remote organ injury is multifactorial including the intracellular signaling pathways which promote these events. Further studies including prevention techniques and will help to prevent remote organ effects of ischemia reperfusion injury following kidney transplantation.

5. Prevention of ischemia reperfusion injury

The renal transplantation is the only definitive treatment for patients with end stage kidney disease. Advances in immunology and success in surgical technique provide almost 95 % graft survival for the first year in living related kidney transplantation. However, the delayed graft dysfunction following kidney transplantation is a main problem affecting long term graft survival (Jassem et al 2002). Ischemia reperfusion injury induces acute renal failure which is very crucial for transplanted kidney survival. At present it is not possible to prevent acute renal failure following transplantation. Success at minimizing ischemic injury

should be aimed. The organ shortage worldwide has increased the interest about drugs, perfusion solutions and perfusion methods to minimize ischemia reperfusion injury. Prevention attempts should begin when a potential donor is determined. It is especially important for suboptimal kidney donors.

The fundamental concerns are to keep the donor hemodynamically stable, to prevent the extent of tubular epithelial cell injury of the kidney following an ischemic insult and to improve its recovery if injury occurs.

Any attempt to prevent renal ischemia is required. Many agents including calcium channel blockers like diltiazem, nifedipine or verapamil; prostaglandins like prostacyclin; thyroid hormone; xanthine oxidase inhibitors like allopurinol or oxypurinol; hydroxyl radicals like dimethylthiourea; ATP-MgCl₂ can be used either alone or in combination to modify the effects of ischemia reperfusion (Finn 1990).

The harvested kidneys should be preserved using iced perfusion solutions like Eurocollins or University of Wisconsin. Immunosuppression is started perioperatively. Treatment of ischemic reperfusion injury to allografts with the free radical scavenger superoxide dismutase during kidney transplantation significantly reduced the incidence of acute rejection episodes and early immune-mediated graft loss with remarkably improved the long-term graft outcome (Land 2005)

A significant portion of the damage sustained by the ischemic kidney occurs not during the period of ischemia, but rather during and following reperfusion. The major affected site is tubular epithelial cells. The success of agents in minimizing renal injury is not increasing renal blood flow but promoting and preserving cell viability.

Hypothermia drops oxygen consumption in the kidney. At temperatures of 6° C to 10° C—the temperature range at which human cadaveric kidneys are perfused prior to transplantation—metabolism is reduced by 90% to 95% (Finn 1990 as cited as Brown & Brengelmann 1965). Cooling will prevent rapid loss of mitochondrial activity and its ability to transport electrons.

In kidney transplantation, free oxygen radicals promotes inflammation and apoptosis triggering alloimmunity against the allograft. In a prospective randomized double-blind placebo-controlled trial, kidney-transplanted, cyclosporine-treated patients received 200 mg human recombinant superoxide dismutase during surgery to prevent and ablate free oxygen radical-mediated reperfusion injury of the graft. Although early function of renal allografts could not be improved by this method, the incidence of first degree acute rejection episodes and acute irreversible allograft rejection were significantly reduced following allogeneic kidney transplantation.

Superoxide-radical-induced cytotoxicity appears largely to depend on the subsequent production of hydroxyl radical. Histidine, tryptophan, ascorbate, and alphas-tocopherol are natural hydroxyl radical scavengers. When lipid peroxidation by free radicals occurs, malondialdehyde, conjugated dienes, hydroperoxides, and short alkanes such as methane, ethane, and pentane are formed. The infusion of ATP, ADP, or AMP are equally effective in promoting early recovery, rather than lessening the initial injury (Land 1999).

The mode of action of superoxide dismutase is blocking both radical mediated and radical dependent (via OH, ONOO₂, H₂O₂ generation) pathways leading to cellular injury during reperfusion. Ischemia reperfusion injury to hearts has been almost completely prevented in hSOD1-transgenic mice (Land 1999 as cited Zweier et al. 1994). This can lead to the chance of successful transplantation of organs from DAF-transgenic pigs to patients would be greater if those animals are also transgenic for the human SOD1 (Land 1999).

6. Conclusion

Ischemia and reperfusion have been a natural step during kidney transplantation. Repair and regeneration process including cellular apoptosis, autophagy, and necrosis follows ischemia reperfusion injury. The final result is directly related to early and late function of the transplanted kidney.

Every transplanted kidney is a damaged organ, and drugs can be used either alone or in combination to modify the effects of ischemia reperfusion besides perfusion solutions and perfusion methods. Further investigations are required to eliminate the effects of ischemia reperfusion injury during kidney transplantation.

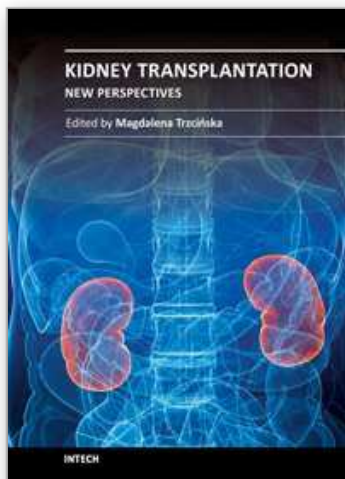
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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and that's why conscious educational efforts are still needed for kidney transplantation, for many people being the only chance for an active lifestyle and improved quality of life, to win common social acceptance and stop triggering negative connotations. Apart from transplantation controversies piling up over years transplantologists also have to face many other medical difficulties. The chapters selected for this book are of high level of content, and the fact that their authors come from many different countries, and sometimes even cultures, has facilitated a comprehensive and interesting approach to the problem of kidney transplantation. The authors cover a wide spectrum of transplant-related topics.

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