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The Impact of Ischemia and Reperfusion Injury in Kidney Allograft Outcome

Valquiria Bueno
UNIFESP – Federal University of São Paulo
Brazil

1. Introduction

Acute kidney injury (AKI) is characterized by a relatively sudden decrease in the production, processing, and excretion of ultrafiltrate by the kidney (decrease in glomerular filtration rate – GFR). Acute kidney injury (AKI) caused by ischemia and reperfusion injury (IRI) is a common event in transplantation and 20% to 80% of kidneys from deceased donors can present delayed graft function (DGF) depending on the injury extent (Perico et al., 2004). After transplantation it could be expected immediate renal function, slow recovery function, non-oliguric acute tubular necrosis (ATN), total anuria. Delayed graft function (DGF) is defined by transplant centers as: the need of dialysis (at least one session) during the first week post-transplantation (Koning et al., 1997), early urine output lower than 1200mL/day or no decrease in serum creatinine within 48h (Shoskes et al., 2001), creatinine clearance lower than 10mL/min (Giral-Classe et al., 1998), creatinine at day 10 higher than 221μmol/L (Cosio et al., 1997).

Delayed graft function has been considered an independent predictor of graft loss since multivariate analysis showed a relative risk of graft loss 2.9 times greater for DGF than for kidneys with immediate function (Halloran et al., 1988). The US Renal Data System (37,000 primary cadaver transplants) showed a relative risk of 1.53 for 5-year graft loss in association with DGF (Ojo et al., 1997). In cadaver transplants (1994-1998 in USA) the half-life of kidneys with DGF was 7.2 years whereas in kidneys with immediate function it was 11.5 years (Halloran et al., 2001). In the presence of rejection DGF's effect is even stronger and kidney graft half-life decreases from 9.4 to 6.2 years (Shoskes et al., 1998). Kyllönen et al. (2000) showed in a follow-up of 1047 cadaveric kidney transplants performed at University of Helsinki that 5-years graft survival was 60% in patients presenting DGF and rejection, 73% in patients with rejection, 77% in patients with DGF and 88% in patients without both risk factors. They concluded that DGF was a significant factor affecting long-term graft survival, both through and independent of acute rejection. In 10-years of transplantation follow-up Troppman et al. (1999) observed 64% of graft survival in patients without DGF or rejection episodes, 44% in patients with DGF, 36% in patients with rejection, and 15% in patients presenting both risk factors.

A range of factors could lead to DGF such as organ procurement (i.e. kidneys from non-heart-beating donors), donor characteristics (i.e. donors older than 55 years), period of ischemia, recipient historic (i.e. number of recipient's previous transplants), renal toxicity, ureteral obstruction, among others. Since DGF is considered an independent risk for graft

loss and one of the factors inducing DGF is ischemia and reperfusion we will focus this chapter on the impact of ischemia and reperfusion in kidney allograft outcome.

2. Ischemia and reperfusion injury

Nankivell & Chapman (2006) conclude in their review that kidney damage after transplantation is mediated by alloimune, ischemic and inflammatory stimuli causing tubular injury in association with profibrotic healing response. In addition to the changes in kidney histology be multifactor post-transplantation, the underestimation of this organ injury by serum creatinine measurement make complex the dissection of the steps during kidney damage. Therefore, biopsy histology is still the gold standard technique to evaluate clinical kidney damage after transplantation. Sequential studies of biopsies show early tubulointerstitial damage followed by later microvascular and glomerular changes with progressive fibrosis and atrophy (Solez et al., 1998; Kuypers et al., 1999, Cosio et al., 1999).
Tubulointerstitial damage begins soon after transplantation due to ischemia-reperfusion injury and the resolution of this process is crucial for kidney outcome. The tubulointerstitium is an essential component of a functioning kidney as it accounts for 95% of a kidney by weight, performs almost all of the metabolic work, and is responsible for salt and water balance, potassium excretion, acid-base control, small protein catabolism, and hormone production such as erythropoietin (Nankivell et al., 2003).
The major events affecting the tubulointerstitium are listed as it follows:

- Oxygen deprivation due to ischemia induces early ATP depletion which stops ATP-dependent transport pumps, resulting in mitochondrial swelling. Mitochondrial swelling results in outer membrane rupture, with release of mitochondrial intermembrane proteins. Caspase 1 or interleukin-1 converting enzyme (ICE) cleaves interleukin (IL)-1b. IL-1b is a pro-inflammatory cytokine, and can induce renal tubular epithelial cells to secrete chemokines such as keratinocyte-induced chemoattractant (KC), macrophage inflammatory protein (MIP)-1a, or RANTES (Furuichi et al., 2002).
- Hypoxia inducible factor (HIF-1, HIF-2, HIF-3), HIF-3 may be a negative regulator of hypoxia-inducible genes expressed by HIF-1 and HIF-2 (Nangaku et al., 2008). HIF-1 is unstable under normal conditions but it is stable and works under hypoxic conditions (Huang et al., 1996; Salceda & Caro, 1997). Many genes encoding for cytokines and growth factors are induced by HIF-1 activation (El Awad B et al., 2000; Zhou & Brune, 2006).
- Oxygen-derived free radicals and in particular hydrogen peroxide, which is a source of oxygen-derived free radicals after IR injury, has been reported to induce TNF-α production by activating p38 mitogen-activated protein kinase (MAPK) (Meldrum et al, 1998).

Ischemia injury begins with the cessation of arterial blood flow and immediate oxygen deprivation in cells (i.e., hypoxia with accumulation of metabolic products). In the kidney, decreased blood supply is associated with flow diversion from cortex to medulla which preserves oxygenation of the metabolically vulnerable medulla at the expense of cortical perfusion and glomerular filtration (Woolfson et al., 1994). Sensitivity to hypoxia or ischemia has been demonstrated in both proximal tubules (Shanley et al., 1986) and their thick ascending limbs (Brezis et al., 1985).
Severe reduction of renal blood flow causes cell damage both by the high-energy phosphate depletion and the subsequent failure to maintain physiological ion gradients across the cell

membrane. However, the major injury to the ischemic organ occurs during the reperfusion phase in which the blood flow returns to the ischemic tissue. Reperfusion is associated with free radical generation leading to lipid peroxidation, polysaccharide depolymerization and deoxyribonucleotide degradation. Injured endothelial cells fail to vasodilate underlying vascular smooth muscle, release potent vasoconstrictors and swell which leads to increased permeability (Woolfson et al., 1994).

Following kidney IRI, the coordinated action of cytokines/chemokines, reactive oxygen intermediates and adhesion molecules causes a cascade of events leading to endothelial cell dysfunction, tubular epithelial cell injury and activation of both tissue-resident and kidney infiltrating leukocytes (Bonventre & Weinberg, 2003; Li & Okusa, 2006).

2.1 Kidney-resident cells can express markers of activation and thus generate inflammatory responses

Toll-like receptors (TLRs) are a family of transmembrane proteins expressed in monocytes, macrophages, dendritic cells, T-and B cells, and neutrophils. TLRs expression by primary culture of mouse cortical renal epithelial cells was first reported by Tsuboi et al. (2002). Renal tubule cells from mouse, rat, and human have been shown to express TLR2 and TLR4 (Wolfs et al., 2002; Yang et al., 2006; Chowdhury et al., 2006; Chassin et al., 2006; Shigeoka et al., 2007; El-Achkar et al., 2006; Bäckhed et al., 2001; Samuelsson et al., 2004). The activation of TLRs can be initiated by pathogens and also by a "sterile" inflammatory process mediated by DAMPs (damage associated molecular pattern molecules). DAMPs are endogenous constituents released by damaged/necrotic cells (heat shock proteins, high mobility group box 1 – HMGB1, fibronectin, heparan sulfate, hyaluronic acid) and components of the extracellular matrix released by proteases to which TLR2 and TLR4 bind.

TLR2 and TLR4 constitutively expressed in resident kidney cells are upregulated after IRI (Wolfs et al., 2002; Kim et al., 2005). TLR cell surface activation triggers an intracellular cascade of events resulting in the release of NF-κB from IκB, allowing NF-κB to translocate from cytoplasm to the nucleus and mediate an increase in inflammatory genes expression which leads to pro-inflammatory responses (Liew et al. 2005; O'Neill, 2006).

Lassen et al. (2010) propose that ischemia reperfusion-induced reactive oxygen species (ROS) activates tubular epithelial cells to release DAMPs which activate TLRs signaling and the subsequent production of proinflammatory cytokines and chemokines either by intrinsic renal cells and intrarenal antigen presenting cells (APCs). As a consequence leukocytes are attracted to the kidney, accumulate in this site, get activated and produce pro-inflammatory cytokines. (Li et al., 2007; Kelly et al., 1996; Wu et al., 2007; Kielar et al., 2005).

IRI causes damages in endothelial cells which in turn increase vascular permeability (Sutton et al., 2003; Brodsky et al., 2002) and the expression of adhesion molecules (Kelly et al., 1996) contributing thus for leukocyte migration to the kidney. Both E-selectin and intercellular adhesion molecule-1 (ICAM-1) on peritubular capillary cells play crucial roles in IRI.

Mice submitted to 32 minutes of bilateral renal pedicles clamp showed a maximum kidney E-selectin expression 24 hours later when renal tissue was evaluated by Western blot. Moreover, the immunostaining localized E-selectin in the endothelium of the peritubular capillary plexus. Administration of anti-E-selectin or use of E-selectin deficient mice was

associated with lower creatinine concentrations at 24 hours indicating a potential therapeutic perspective for this molecule (Singbartl & Ley, 2000).
The evaluation of 49 renal transplant patients with mean cold ischemia time of 27 hours showed that 3 minutes after kidney graft reperfusion the renal vein presented concentrations of E-selectin, VCAM and ICAM which correlated positively with hypoxanthine concentrations. This correlation may be associated with the release of hypoxanthine by the graft as an ischemia marker reflecting metabolic changes in renal tissue during reperfusion (Domanski et al., 2009).
The inflammatory microenvironment in the kidney is closely associated with the functional and structural renal changes occurring in this organ after IRI.

2.2 Cells associated with IRI

2.2.1 Dendritic cells

Dendritic cells (DCs - $CD11c^+$) and class II major histocompatibility complex (MHC Class $II)^+$ DCs are the most abundant leukocyte subset residing in the normal mouse kidney (Li et al., 2008; Soos et al., 2006) suggesting an important role in renal immunity and inflammation. TNF-α, IL-6, MCP-1 and RANTES (pro-inflammatory cytokines/chemokines) are produced by renal DCs after IRI, and depletion of DCs prior to IRI significantly reduced the kidney levels of TNF-α (Dong et al., 2007).

2.2.2 Neutrophils

Neutrophils inhibition has been shown in some studies to attenuate renal injury after IRI (Kelly et al., 1996), whereas other studies failed to find a protective effect of neutrophil blockade or depletion (Thornton et al., 1989). Many factors affecting neutrophil infiltration or activation including neutrophil elastase, tissue-type plasminogen activator, hepatocyte growth factor, and CD44 have been suggested to contribute for the renal damage following IRI (Hayama et al., 2006; Roelofs et al., 2006; Mizuno et al., 2005; Rouschop et al., 2005). Despite discrepancies in data provided by different research groups, it is likely that neutrophils participate in inducing renal injury by plugging renal microvasculature and releasing oxygen-free radicals and proteases.

2.2.3 Macrophages

Macrophages infiltrate the injured kidney early within 1 hour of reperfusion, and this infiltration is mediated by CCR2 and CX_3CR1 signaling pathways (Oh et al., 2008; Li et al., 2008). Analysis of kidney infiltrating macrophages by flow cytometry demonstrated that these leukocytes are significant producers of the cytokines IL-1α, IL-6, IL-12p40/70 and TNF-α (Li et al., 2008).

2.2.4 Natural Killer

Natural Killer (NK) cells have recently been reported to infiltrate the post-ischemic kidney by 4 hours of reperfusion. IRI induced the expression of an NK cell-activating ligand (Rae-1) on tubule epithelial cells (TECs) and *in vitro* studies demonstrated that the interaction of the NKG2D receptor on NK cells with Rae-1 on TECs causes perforin-dependent lysis of cultured kidney cells. Antibody-mediated depletion of NK cells inhibited IRI in wild-type (WT) mice and adoptive transfer of WT, but not perforin KO, NK cells into a T, B and NK cell-deficient mouse enhanced IRI (Zhang et al., 2008).

2.2.5 Invariant Natural Killer T

Invariant Natural Killer T (iNKT) cells are a unique subset of T lymphocytes with surface receptors and functional properties shared with conventional T cells and NK cells. In contrast to conventional T cells, iNKT cells are activated by endogenously released glycolipid antigens. A recent finding is that the number of IFN-γ-producing iNKT cells in the kidney is significantly increased by 3 hours of reperfusion compared to sham-operated mice. Also, blockade of NKT cell activation with the anti-CD1d mAb, NKT cell depletion with an anti-NK1.1 mAb in WT mice, or use of iNKT cell deficient mice (Jα18$^{-/-}$) inhibited the accumulation of IFN-γ-producing neutrophils after IRI and prevented AKI (Li et al., 2007).

2.2.6 T lymphocytes

In the early stage of IRI, T cells may become activated through antigen-independent mechanisms by inflammatory cytokines and reactive oxygen intermediates (Bacon et al., 1995). T cell trafficking was observed as early as 1 h after IRI and decreased at 24 h following IRI (Noiri et al., 2009; Ascon et al., 2006). T cell recruitment influences proinflammatory cytokine production, neutrophil trafficking, and progression to fibrosis (Burne et al., 2001). Moreover, T cells also influence vascular permeability in early ischemic AKI (Saito et al., 2009). Increased numbers of activated and effector-memory T cells were found in the postischemic kidneys as late as 6 weeks after IRI, suggesting that T cells are also involved in long term structural changes of postischemic kidneys (Ascon et al., 2008).

2.3 Histology changes in kidney after IRI

IRI is associated with several complexes events such as negative impact in capillary density (Basile et al., 2001) and increase of the vascular permeability which interferes with the protective barrier among circulating elements and parenchyma cells. These factors induce the no-reflow phenomenon and leads to inflammation (Cicco et al., 2005; Sutton TA, 2009).

Jayle et al. (2007) showed that in pig kidney autotransplant model the development of chronic fibrosis and subsequent renal failure were associated with the severity of IRI with more damage occurring in kidneys submitted to 60 or 90 minutes of IRI than to 45 minutes. Using the same model Thuillier et al. (2010) evaluated 60 minutes of renal pedicle clamping, kidney removal and preservation for 24 hours in UW solution followed by autotransplantation and showed that 3 months later the GFR was still significantly lower and the proteinuria was increased. Grafts presented a significant amount of interstitial fibrosis and tubular atrophy besides of T and ED1+ cells infiltration. Authors concluded that IRI has the ability to induce chronic adaptive inflammation response, even in autologous grafts. Moreover, even 6 weeks later of prolonged ischemia (unilateral renal pedicle clamp for 60 minutes) in the absence of transplantation it was possible to observe kidney shrunken in size with loss of tubular architecture (dilatation of tubules and cyst formation). It was also found infiltration of phagocytes, neutrophils and T cells suggesting long-term kidney inflammation (Burne-Taney et al., 2005).

Williams et al. (1997) showed that rats submitted to 45 minutes of bilateral renal pedicle clamp presented a peak of increased serum creatinine 24 hours later which was in accordance with the highest renal myeloperoxidase activity (and indicator of neutrophil infiltration) and massive amount of proximal convoluted tubule cells necrosis. Despite the return of creatinine to normal levels at 1 week later, atrophic tubules and focal fibrosis were still observed suggesting permanent tubular loss.

It has been shown that hypoxic stress induces apoptosis of renal proximal tubular cells via mitochondria-dependent and –independent pathways, partly by activation of caspase-3 (Edelstein et al., 1999). Clinical and experimental models demonstrate that immunosuppressive drugs can impair tubular cells proliferation in replacement to those in apoptosis.

Lui et al. (2006) observed that mice treated with Rapamycin from day -1 and submitted to 45 minutes of bilateral renal pedicles clamping presented 24 hours later significantly increased levels of creatinine. Moreover, renal tubular cells showed generalized swelling and vascuolization besides of very low numbers of PCNA-positive nuclei cells. These factors were normalized on day 3 except for PCNA which increased only on day 7 suggesting that early after IR Rapamycin impairs renal function and retards the proliferative response of the renal tubular cells.

Sirolimus exposure in recipients of cadaveric kidneys (mean of cold ischemia time = 20 hours) experiencing DGF showed strong association with prolonged time for the recovery of the graft function. This finding indicates that sirolimus impairs the kidney's ability to recovery from injury (McTaggart et al., 2003).

Novick et al. (1986) showed that cadaveric transplants with mean preservation time of 37 hours presented one-year actuarial graft survival of 78% in ALG (azathioprine – prednisone - antilymphocyte globulin) versus 48% in CsA (prednisone- cyclosporine) immunosuppressive protocol. The difference was attributed to the large number of primary nonfunctioning grafts in CsA group probably due to the effect of CsA's nephrotoxicity superimposed on renal ischemia incurred prior to transplantation.

2.4 Ischemic acute kidney injury (AKI) influences the choice of the immunosuppressive therapy after transplantation

Nankivell et al. (2003) evaluated biopsies of 120 patients maintained on Cyclosporine-based immunosuppression 5 years post-transplantation and found that 66% of them presented moderate-to-severe interstitial fibrosis and 90.3% presented arteriolar hyalinosis. Authors proposed two phases of chronic allograft nephropathy: an early fibrogenic phase attributed to ischemia-reperfusion injury and a late phase with fibrosis and arteriolar hyalianosis generated by cyclosporine (CsA) toxicity. On the other hand, Stegall et al. (2010) showed in 296 biopsies that the prevalence of moderate/severe histology changes at both 1 and 5 years post-transplantation was less than 20% including fibrosis and hyalinosis in recipients treated with a triple therapy (Tacrolimus, MMF and Azatioprine, or Sirolimus in the CNI-free protocol). Authors also found that the most important variable associated with moderate/severe fibrosis at 5 years was delayed graft function (DGF).

Despite of the controversy in how significant is the hazard added by the immunosuppression (past immunosuppressive protocols versus new immunosuppressive era) to the kidney function and histology it seems to be a consensus that DGF is an independent risk at any of the immunosuppressive protocols evaluated. This has been confirmed recently by Snoeijs et al. (2011) in MMF or SRL protocols when 8 recipients of kidneys from deceased donors with ischemia and reperfusion injury (DCD) were compared with 8 recipients of kidneys from living donors with minimal ischemic injury (LD). Delayed graft function was 70% in recipients of DCD kidneys whereas 100% of patients receiving LD kidneys showed immediate graft function. Creatinine clearance was significantly lower in recipients of DCD kidneys than in recipients of LD kidneys whereas the fractional excretion

of sodium was higher in DCD group. In addition, kidneys from DCD donors presented post-transplantation early necrotic tubular epithelial cell death and systemic immune response activation.

Boratynska et al. (2008) showed that patients receiving kidney transplants with cold ischemia time longer than 24 hours and treated with a SRL (SRL + CsA + Prednisone, n=23) or CsA (Azathioprine + CsA + Prednisone, n=23) protocol presented DGF in 39% and 35% of cases respectively. Moreover, the duration of DGF and the decrease in serum creatinine were prolonged in the SRL protocol whereas biopsies from both groups presented loss of the brush border in tubular epithelial cells. One and 5-year graft survival were 100% and 87% in SRL and 95% and 74% in CsA protocols showing improved renal graft survival in patients treated with SRL. Serum creatinine level at the 12th month was higher in patients with DGF independent of the immunosuppressive protocol.

Experimental models have contributed extensively to the better knowledge in IRI, immunosuppressive regimen and kidney damage. Moreover, clinical findings are in line with experimental models as it follows:

Ninova et al. (2004) showed in a rat model that at early time point (14 days) few signs of nephrotoxicity developed when unilateral nephrectomy was performed and animals were treated with Tacrolimus or Sirolimus. However, when kidneys were submitted to IRI due to transplantation, there was increase in serum creatinine, interstitial fibrosis, vacuolization and inflammation. It was also found, intragraft expression of TGF-β and α-SMA indicating a profibrotic environment. These results suggest that IRI plays a significant role in drug-induced nephrotoxicity.

Delbridge et al. showed that rats submitted to monolateral renal clamp for 45 minutes and nephrectomy of the contrateral kidney presented 30 days later a serum creatinine (SCr) still significantly higher than control rats. The treatment with FTY720 alone (1mg/kd) decreased SCr to control levels while CsA (15mg/kg) potentiated the increase in SCr. However, the decrease in SCr was observed when FTY720 was administered in association with CsA suggesting a protective effect for the treatment with FTY720. The same was observed for proteinuria, kidney fibrosis and levels of serum TGF-β1 (Delbridge et al., 2007). Using the same model and treating rats with MMF (20mg/kg/d) Sabbatini et al. (2010) showed 6 months after IRI that the glomerular filtration rate (GFR) was similar when non-treated animals (GFR=0.50) were compared with those treated with MMF (GFR=0.49) which was significantly lower than in normal uninephrectomized animals (GFR=0.87). Even though MMF significantly reduced the early kidney inflammatory process, renal histology in treated rats was similar to that of untreated animals showing 28% and 34% respectively of tubular necrotic cells.

3. Conclusion

Ischemia reperfusion injury is a common event in kidney cadaveric transplantation and leads to delayed graft function. The choice of the immunosuppressive protocol should consider that the early administration of drugs such as CNIs and Sirolimus could retard the recovery of kidney function and structure.

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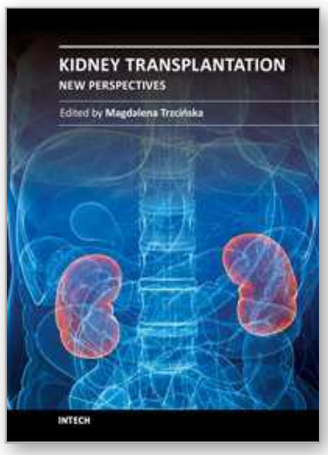
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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and thatâ€™s why conscious 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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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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