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Oxidative and Nitrosative Stress in the Ischemic Acute Renal Failure

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1. Introduction

Ischemic injury to the kidney is the most common cause of acute kidney injury. Despite intensive basic research and in critical care for decades it is still associated with high mortality rates of ~50% in the intensive care unit. It is observed in a variety of clinical situations such as cardiac arrest with recovery, organ transplantation, or heminephrectomy. Postischemic acute kidney injury is characterized by an abrupt decrease in glomerular filtration rate (GFR) (the hallmark feature of acute kidney injury), and increased renal vascular resistance that determines a persistent reduction in renal blood flow (RBF) and tubular injury. However, the pathophysiological mechanisms responsible for the postischemic renal injury and the profoundly depressed renal function remain incompletely understood. The accumulated data in the literature are compatible with the hypothesis that ischemic acute kidney injury is essentially a phenomenon of altered renal hemodynamics linked critically to endothelial cell dysfunction caused by the production of high levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to decreased nitric oxide availability as a consequence of its destruction to form peroxynitrite, associated with an intracellular energy store depletion. The oxidative and nitrosative stress will produce lipid peroxidation, oxidative DNA damage and modification and inactivation of proteins that originates an inflammatory reaction characterized by endothelial activation and injury, enhanced endothelial cell-leukocyte adhesion, leukocyte entrapment, and a reduction in microvascular blood flow mainly affecting the renal outer medulla as indicated by the marked vascular congestion typically observed in this zone of the kidney. On the other hand, and depending on the severity of renal ischemia, tubular epithelial cells will undergo a varying degree of necrosis or apoptosis with tubular obstruction followed by both an anatomical and functional recovery. The way in which vascular and tubular epithelium recover determines the final status of the renal function, ranging from full recovery to chronic renal failure and ultimately to end-stage renal disease. Because of the importance of endothelial cells in this process, emphasis will be placed on the involvement of oxidative and nitrosative stress in causing endothelial dysfunction, the sources of oxygen and nitrogen reactive species, and the interactions between them, specially superoxide anion and nitric oxide because together they form peroxynitrite, a potent oxidant and nitrosant agent. Among other factors, the severity of acute kidney injury is mainly determined by the duration of the ischemia. Special attention will be paid to the vascular and hemodynamic

changes produced in the outer medulla during renal ischemia/reperfusion, because this renal zone is physiologically nearly hypoxic. The role of heme oxygenase system and the gender differences in the susceptibility to ischemic acute renal failure will be also be revised

2. Morphologic and hemodynamic changes in ischemic acute kidney injury

In apparent disagreement with the severe impairment of renal function, histologic changes in acute kidney injury are relatively subtle, and necrosis (if present) is restricted to the outer medullary region of the kidney. Morphologic changes include effacement and loss of proximal tubule brush border, patchy loss of tubule cells with apoptosis limited to both proximal and distal tubules, focal areas of tubular dilation with distal tubular casts (consisting of Tamm-Horsfall protein and cellular debris) and areas of regeneration. Peritubular capillaries present endothelial injury with enhanced expression of adhesion molecules (e.g. intercellular adhesion molecule-1, E-selectin, P-selectin) and cell swelling that promote adhesion of platelets to endothelium, with subsequent leukocyte adhesion and adhesion of platelets to neutrophils which are then aggregated and trapped in narrow peritubular capillaries causing vascular congestion, with cessation and even reversal of blood flow (Brodsky et al, 2002; Yamamoto et al, 2002). Endothelial injury also iniciates an inflammatory response that can be enhanced by tubular cells through the generation of proinflammatory cytokines and chemotactic cytokines (Bonventre & Zuk, 2004; Friedewald & Rabb, 2004; Schrier et al, 2004; Devarajan, 2006).

Functionally, the ischemic insult is followed by an intense and persistent renal vasoconstriction that significantly reduces renal blood flow to ~50% of normal (Cristol et al, 1993; Lieberthal et al, 1989), and has dramatic consequences in the renal outer medulla due to the fact that it is physiologically on the verge of hypoxia. Through a poorly understood mechanism, this acute reduction in outer medullary blood flow is followed later by a situation of chronic hypoxia (Basile et al, 2001; López Conesa et al, 2001). The increased basal vascular tone is also accompanied by increased reactivity to vasoconstrictors and a decreased response of arterioles to vasodilators, with loss of autoregulation of renal blood flow and abnormal vascular reactivity characteristic of postischemic acute kidney injury (Bonventre & Weinberg, 2003). These changes have been attributed to altered prostaglandins synthesis, to the generation of reactive oxygen and nitrogen species, and/or to activation of inflammatory responses to ischemia and it seems to be critically linked to endothelial dysfunction and to the increased generation of reactive oxygen and nitrogen species (oxidative and nitrosative stress) with a decrease in nitric oxide availability.

3. Temporal course of ischemic acute renal failure

Clinically, ischemic acute renal failure has classically been divided into the "Initiation", "Maintenance" and "Recovery" phases (Sutton et al, 2002; Devarajan et al, 2006). Sutton et al (2002) proposed a fourth phase, the "Extension" phase.

The "Initiation" phase begins when cellular ATP content becomes depleted as a consequence of anoxia, with the resultant tubular epithelial, smooth muscle and endothelial cell injuries characterized by disruption of actin cytoskeleton that produces structural and functional tubular alterations, and renal vasculature abnormalities. The severity and extent of these injuries will be determined by the degree and duration of ischemia. From a

functional point of view epithelial and endothelial cells become "activated" up-regulating a number of cytokines and chemokines such as interleukins -1, -6, and -8, monocyte chemoatractant protein-1, and tumor necrosis factor alpha, thus triggering the inflammatory cascade. A key event in the "activation" of endothelial cells is a decrease in nitric oxide production.

The "Extension" phase is determined by two major events, a state of continued hypoxia with decreased blood flow, stasis and red and white blood cells accumulation mainly affecting outer medulla, and an inflammatory response. Thus, endothelial dysfunction in this phase plays a key role in the continued ischemia of tubular cells as well as in the inflammatory response observed in ischemic acute renal failure. As a consequence of these changes, apoptosis and necrosis of tubular cells (mainly affecting outer medulla) is observed and glomerular filtration rate continues falling.

During the "Maintenance" phase cells undergo repair (with apoptosis, proliferation and migration of cells) to re-establish and maintain cell and structure integrity with a slow improving in cellular and tubular function. Glomerular filtration rate is maintained to a level determined by the severity and duration of ischemia. Renal blood flow recovers approaching preischemic levels. During the "Recovery" phase a slowly and progressive improvement towards normality is taking place.

During all these phases the initial endothelium dysfunction and its posterior recuperation are of key importance to overall recovery.

4. Importance of renal medulla in the renal response to ischemia

4.1 Susceptibility of renal medulla to hypoxia

Many studies indicate that the severity of post-ischemic renal injury depends on the state of persistent hypo-perfusion of the renal outer medulla. The susceptibility of renal medulla to hypoxia lies in the fact that: a) renal arteries and veins run strictly parallel and in close contact with each other over long distances, allowing oxygen to diffuse from the arterial to the venous system before it has entered the capillary bed; b) tubular segments of the outer medulla have a limited capacity for anaerobic energy generation and, thus, depend on its oxygen supply to maintain active transtubular sodium and the reabsorption and secretion of solutes. These facts are particularly relevant in the tubular segments of the outer medulla (S3 segment of proximal tubules and medullary thick ascending loop of Henle) where the combination of limited oxygen supply (pO_2 < 25 mmHg) and a high oxygen demand makes the outer medulla to be physiologically on the verge of hypoxia (Brezis & Rosen, 1995; Zhang & Edwards, 2002). A variety of physiologic mechanisms are involved in protecting the outer medulla against hypoxic injury, including nitric oxide, prostaglandins, heme oxygenase-1 and adenosine, all of which enhance medullary blood flow while down-regulate active tubular transport of sodium and solutes (Brezis et al, 1989; Brezis et al, 1991; Knight & Johns, 2005; Rosenberger et al, 2006). A number of studies have shown that nitric oxide is a main regulator of medullary blood flow. Inhibition of nitric oxide production is followed by a decrease in medullary pO_2 in control animals and medullary blood flow (Cowley et al, 2003; Fenoy et al, 1995; López-Conesa et al, 2001; Nakanishi et al, 1995; O´Connor et al, 2006; Rodríguez et al, 2010; Rosenberger et al, 2006). Therefore, the

functional status of the renal medullary nitric oxide system after the ischemia-reperfusion injury is believed to be a major determinant in the development of renal failure.

4.2 Outer medulla and ischemia-reperfusion

The importance of outer medulla in the renal response to an ischemic event has been demonstrated by several studies. Basile et al (2001) observed that renal ischemia results in permanent damage to peritubular capillaries and influences long-term function. They measured a 30-50% reduction in peritubular capillary density in the outer medulla at 4, 8 and 40 weeks after ischemia and tubulointerstitial fibrosis with increased transforming growth factor-1 expression at 40 weeks. Moreover, they also demonstrated an increase in 2-pimonidazole staining (a hypoxia-sensitive marker) in outer medulla accompanied by proteinuria, interstitial fibrosis and renal functional loss. They also observed that chronic L-arginine administration in drinking water increased total renal blood flow, decreased 2-pimonidazole staining and attenuated or delayed the progression of chronic renal insufficiency after recovery from acute ischemic injury (Basile et al, 2003). On the other hand, López-Conesa et al (2001) reported that an antioxidant ameliorated the renal failure and prevented the outer medullary vasoconstriction observed after 45 min of renal ischemia, effects that seem to be dependent on the presence of nitric oxide and the scavenging of peroxynitrite. Taken together, data from these studies strongly suggest that the renal failure that follows an ischemic event is directly related to alterations in outer medullary blood flow and that these changes seems to be dependent on free radical production and nitric oxide bioavailability.

5. Free radicals in acute renal injury

Free radicals are small, diffusible molecules that have an unpaired electron and tend to be reactive and can participate in chain reactions in which a single free radical event can be propagated to damage multiple molecules. The generation of oxygen free radicals is mainly restricted to mitochondria. In a controlled process 4 electrons from the electron transport chain are added to molecular oxygen yielding two water molecules. These electrons additions generate sequentially superoxide anion, hydrogen peroxide and the hydroxyl radical before the addition of the final electron to produce water. Reactive oxygen species can be also endogenously generated from other enzymes such as NAD(P)H-oxidases, xanthine oxidases, cyclooxigenases, lipooxygenases, myeloperoxidases, or uncoupled nitric oxide synthases. Each of these free radicals is able of oxidizing surrounding biomolecules thus generating other potent oxidants such as hypochlorous acid (harnessed by phagocytes for bacterial killing) or peroxynitrite anion (formed by the reaction of equimolecular amounts of nitric oxide and superoxide). However, the idea that the effects of reactive oxygen species on cellular functions are always deleterious is no longer valid because a number of studies have demonstrated that under physiological conditions low concentrations of reactive oxygen species play an important role in the normal regulation of cell and organ function. In this regard Ignarro et al (1988) demonstrated that superoxide dismutase enhanced arterial relaxation induced by the infusion of acetylcholine, indicating that there is a physiological production of a small amount of superoxide that is normally counteracting the vasodilatory effect of nitric oxide. In the kidney, Zou & Cowley (2001) demonstrated a basal generation of superoxide anion in all renal zones with the highest

production in the outer medulla. Nitric oxide is a known renal vasodilator and acts as a natriuretic agent; superoxide has been shown to decrease renal blood flow and sodium excretion (Majid & Nishiyama, 2002; Majid et al, 2004, 2005; López et al, 2003; Makino et al, 2002; Zou & Cowley, 2001). Thus, there is evidence suggesting that superoxide is an important physiologic modulator of endogenous NO activity, counteracting the effects of nitric oxide in the kidney, and that superoxide exerts a tonic regulatory action on renal medullary blood flow.

Under steady-state conditions free radicals are effectively eliminated by antioxidant defense mechanisms that include free radical scavenging enzymes (superoxide dismutase, catalase, or glutathione peroxidase) and abundant radical scavenging chemicals (reduced glutathione, cysteine, vitamins C and E) that prevent almost completely radical chain reactions. However, when present in excess, a condition known as oxidative stress, they exert deleterious effects including lipid peroxidation, oxidative DNA damage and protein oxidation and nitration that collectively lead to progressive endothelial and tubular cells damage described in the precedent section. Generation of high levels of reactive oxygen species during renal ischemia/reperfusion have been confirmed directly (Zweier et al, 1994; Salom et al, 2007) and indirectly by measuring the effects of oxidants on lipids, proteins and DNA and by determining the beneficial effects of free radicals scavenging with antioxidant enzymes like superoxide dismutase or catalase or with antioxidants allopurinol (a xanthine oxidase inhibitor), tempol (an superoxide dismutase mimetic), N-acetyl-L-cysteine (an antioxidant), or dimethylthiourea (a hydroxyl radical scavenger)(Chatterjee et al, 2000; López-Conesa et al, 2001; Nitescu et al, 2006; Noiri et al, 2001; Tsuji et al, 2009). However, these compounds also scavenge or inhibit the formation of peroxynitrite ($ONOO^-$) a highly reactive chemical specie derived from nitric oxide and superoxide. Peroxynitrite and other reactive nitrogen species act together with other reactive oxygen species to damage cells, causing what is known as nitrosative stress.

6. Renal vascular endothelium, nitric oxide and acute renal failure

6.1 Vascular endothelium and nitric oxide in renal function regulation

The endothelium is the thin layer of cells that lines the interior surface of blood vessels, forming an interface between circulating blood in the lumen and the rest of the vessel wall. The vascular endothelium regulates vascular permeability, and modulates vasomotor, inflammatory, and haemostatic responses and nitric oxide appears to play a key role in these regulatory functions (Bird, 2011; Michel, & Vanhoutte, 2010). Nitric oxide regulates vascular tone preventing abnormal constriction, inhibits platelet aggregation, the expression of adhesion molecules at the surface of endothelial cells thus inhibiting the adhesion and penetration of white blood cells, and the release and action of endothelin-1 (Michel & Vanhoutte, 2010).

6.1.1 Nitric Oxide System

Nitric oxide is a diatomic free-radical gas synthesized from L-arginine by a family of enzymes called nitric oxide synthases. There are three mammalian nitric oxide synthases isoforms: neuronal (nNOS), inducible (iNOS) and endothelial (eNOS). They share 50–60% homology at the amino acid level and have an N-terminal oxygenase domain with heme-, L-

arginine-, tetrahydrobiopterin (BH4)-binding domains, a central calmodulin (CaM)-binding region, and a C-terminal reductase domain with NADPH, FAD, and FMN binding sites (Stuehr, 1997). Under physiological conditions, the dominant nitric oxide synthase isoform in the vasculature is endothelial nitric oxide synthase, which is dynamically regulated at the transcriptional, posttranscriptional, and posttranslational levels (see Rafikov R et al, 2011 for a comprehensible review of the posttranslational control of endothelial nitric oxide synthase). Nitric oxide synthesis requires binding of the Ca^{2+}/calmodulin complex, but also requires dimerization of endothelial nitric oxide synthase and cofactors binding for activity. In the inactive state, endothelial nitric oxide synthase is located in plasma membrane caveolae bound to inhibitory protein caveolin-1. When activated the increase in Ca^{2+}/CaM releases and dimerizes endothelial nitric oxide synthase and interacts with its associated proteins heat shock protein 90 and Akt, and cofactors in an active complex. This activation process requires phosphorylation/dephosphorylation of the enzyme at different sites of tyrosine (Tyr-81 and Tyr-657), serine (Ser-114, Ser-615, Ser-633, and Ser-1177), and threonine (Thr495). The enzymes cycles between the inactive state bound to caveolin-1 in caveolae to cytoplasma in the activated state. The production of nitric oxide in endothelium cells is induced by mechanical action (shear stress) and by agonists such as acetylcholine, bradykinin, or histamine. Nitric oxide freely diffuses through plasma membrane to the underlying smooth muscles and triggers their relaxation by stimulating soluble guanylate cyclase that increases cyclic guanosine monophosphate levels. Nitric oxide also diffuses to the endothelium surface where inhibits adhesion and aggregation of platelets, modulates the permeability of endothelium, and inhibits endothelium-leukocytes interaction by reducing the expression of adhesion molecules.

Nitric oxide also plays an important role in the regulation of the renal hemodynamic and excretory functions (Romero et al, 1992). Inhibition of nitric oxide synthesis has shown to worsen both cortical and medullary blood flow and oxygenation (Cowley et al, 2003; Brezis et al, 1991)., indicating that nitric oxide is important for the maintenance of renal blood flow after ischemia-reperfusion injury of the renal vascular bed.

6.2 Endothelial dysfunction and acute renal failure – Role of nitric oxide

Ischemia/reperfusion of the kidney is followed by endothelium dysfunction and injury that contribute to the impairment of renal perfusion and chronic hypoxia, with the subsequent epithelial cell injury and decrease in the glomerular filtration rate that are the hallmarks of acute renal failure. Endothelial dysfunction, defined as impaired vasorelaxation in response to endothelium-dependent vasodilators, has been observed during renal ischemia-reperfusion (Brezis & Rosen, 1995; Cristol et al, 1993; Erdely et al, 2003; Kher et al, 2005; Lieberthal et al, 1989; Salom et al, 1998). Cristol et al (1993) and Salom et al (1998) reported renal vasoconstriction and impairment of the vasodilator effect of acetylcholine after acute renal ischemia. They also found that the recovery of renal blood flow observed on reperfusion was prevented by the previous nitric oxide synthesis inhibition. Renal ischemia/reperfusion is accompanied by a persistent reduction in renal blood flow of greater magnitude in the outer medulla. Mechanisms involved in this persistent reduction in renal perfusion are incompletely understood, but it has been observed endothelial cell swelling and detachment with trapping of red blood cells and leukocytes that produce vascular congestion of renal microcirculation especially in outer medulla (Olof et al, 1991;

Hellberg et al, 1990a, 1990b; Mason et al, 1984; Solez et al, 1974). Endothelial dysfunction in the outer medulla could contribute to the tubular epithelial cell injury thus determining a progressive fall in glomerular filtration rate in the initial and extending phases of acute renal failure. The key role of endothelial dysfunction in acute renal ischemia was demonstrated by studies of Brodsky et al, (2002) who transplanted endothelial cells or surrogate cells expressing endothelial nitric oxide synthase into rats subjected to renal artery clamping. Implantation of endothelial cells or their surrogates in the renal microvasculature resulted in a dramatic functional protection of ischemic kidneys. These observations strongly suggest that endothelial cell dysfunction is the primary cause of the no-reflow phenomenon, which, when ameliorated, results in prevention of renal injury seen in acute renal failure.
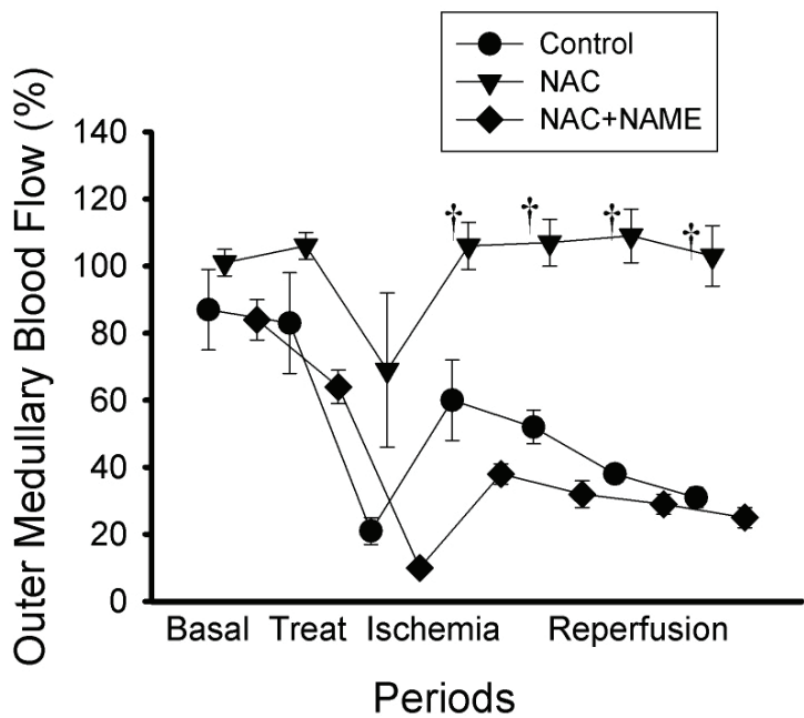
Fig. 1. Outer medullary blood flow during renal ischemia/reperfusion in SD rats.
% Change from the basal period in outer medullary blood flow during renal ischemia/reperfusion (45 min occlusion of renal artery) in Sprague-Dawley rats infused (Treat.) with saline (Control), N-acetyl-L-cysteine (150 mg/kg, as a bolus, plus 715 µg/kg/min) or L-Name (10 µg/kg/min), or L-Name + N-acetyl-L-cysteine).† Significant difference from the same experimental period of the control group (López-Conesa et al, 2001)

Endothelial dysfunction is an early event that is produced when oxygen free radicals are produced on reflow. Tsao et al (1990), Tsao & Lefer (1990) and Lefer & Ma (1991) in cardiac and splanchnic ischemia-reperfusion experiments demonstrated that endothelial dysfunction was related to reoxygenation and not to reflow and that this noxious effect can be prevented when free radical scavengers are infused before reperfusion. In the kidney, an increased free radical production has been demonstrated during reperfusion in *in vitro* (Kadkhodaee et al, 1995; Paller & Neumann, 1991) and *in vivo* experiments (Haraldsson et al, 1992; Nilsson et al, 1993). There is indirect evidence showing that endothelial dysfunction

appears to be due to the generation of oxygen free radicals during reperfusion (Lieberthal, 1997; Salom et al, 1998). When infused before reperfusion, oxygen free radical scavengers exert a beneficial effect by preventing oxygen free radical production during reoxygenation (Baker et al, 1985; Hansson et al, 1990; Nilsson et al, 1993; Salom et al, 1998). In addition, the beneficial effect of some scavengers has been attributed to nitric oxide potentiation (Caramelo et al, 1996; López-Neblina et al, 1996; Salom et al, 1998), suggesting that the inactivation of nitric oxide by free radical is an important factor contributing to postischemic acute renal failure. This hypothesis was tested by López-Conesa et al, (2001) who found that N-acetyl-L-cysteine, a free radical scavenger, ameliorated the renal failure, and prevented the outer medullary vasoconstriction and the increase in plasma concentration of rhodamine 123 (index of peroxynitrite production) induced by renal ischemia. These results suggest that beneficial effects of N-acetyl-L-cysteine seem to be dependent on the presence of nitric oxide and the scavenging of peroxynitrite.

6.3 Ischemic preconditioning

Ischemic preconditioning is a phenomenon induced by brief ischemia and reperfusion periods that renders an organ more tolerant to subsequent sustained ischemia/reperfusion. In preconditioned kidneys, the sustained ischemia produces only small increases in plasma creatinine and in fractional sodium excretion, accompanied by markedly attenuated outer medullary congestion and leukocyte infiltration (Park et al, 2001, 2002). The mechanisms underlying this protective effect against injury are not well known. However, several candidates that could potentially serve as mediators of the preconditioning phenomenon have been identified. One of them, the nitric oxide synthase pathway, seems to be of importance. Park et al (2003) observed that prior ischemia results in prolonged increase in endothelial and inducible nitric oxide synthases (eNOS and iNOS). Torras et al (2002) observed that the protection afforded by ischemic preconditioning is abrogated by the inhibition of iNOS, and reproduced by a nitric oxide donor. Park et al (2003) showed that gene deletion of inducible (but not endothelial) nitric oxide synthase increases the kidney susceptibility to ischemia. In apparent contradiction, Yamasowa et al (2005) found that preconditioning in eNOS$^{+/+}$ mice markedly attenuated the renal dysfunction and improved the histological renal damage that follow ischemia/reperfusion (medullary congestion, intratubular casts or tubular necrosis). Preconditioning also prevented the marked decrease in endothelial nitric oxide synthase activity observed 6 hours after ischemia. (Yamasowa et al, 2005). The effects of preconditioning were abolished by a non-selective inhibitor of nitric oxide synthases, whereas aminoguanidine (a selective inhibitor of the inducible isoform) had no effect. A role for nitric oxide has also been reported by Jefayri et al (2000). Differences in the length of time between the first (preconditioning) and the second ischemic episode may explain differences observed between these studies. Park et al (2003) performed the second ischemia 1, 3, 4, 6, 10, or 12 weeks after the first (preconditioning) ischemia and at that time the expression of inducible but not endothelial nitric oxide synthase was significantly increased and nitric oxide levels before the second ischemia were high due to inducible isoform of the enzyme. In the study of Yamasowa et al (2005) the second ischemia was performed immediately after the preconditioning was finished (5 min). Yamasowa et al found that preconditioning prevents the decrease in endothelial nitric oxide synthase activity and prevented the increase in inducible nitric oxide synthase activity

observed after 6 h of reperfusion. As Nakajima et al (2006) observed an increased production of superoxide in the first day after the ischemia, the inhibition of inducible nitric oxide synthase could theoretically prevent the formation of high levels of peroxynitrite. This could explain why inhibition of inducible nitric oxide synthase before the ischemia reduces renal ischemia/reperfusion injury (Chatterjee et al, 2002; Walker et al, 2000) and why inhibition of inducible nitric oxide synthase before the ischemia prevents renal microvascular hypoxia and inhibition of endothelial isoform aggravates renal function (Legrand et al, 2009). The data of these studies indicate that preconditioning protects the kidney partly by increasing nitric oxide levels due to the increase in endothelial (early protecting effect) or in the inducible nitric oxide synthase activity (long lasting protective effect). The studies of Nakajima et al (2006) who observed a significant attenuation of nitrotyrosine formation, neutrophil infiltration into renal tissues, and renal superoxide production, that were significantly attenuated by the preischemic treatment with a nitric oxide donor. Thus, a better understanding of ischemic preconditioning may help to unravel the underlying mechanisms of protection that mediate this tolerance against injury.

7. Oxidative and nitrosative stress and endothelial dysfunction in ischemic acute kidney injury

Endothelial dysfunction and oxidative stress are the main pathophysiological mechanisms of several diseases such as hypertension, atherosclerosis, dyslipidemia, diabetes mellitus, cardiovascular disease, renal failure and ischemia-reperfusion injury. Reactive oxygen species can modulate cellular function, receptor signals and immune responses in physiological conditions, but when present in excess, they mediate progressive endothelial damage through growth and migration of vascular smooth muscle and inflammatory cells, alteration of extracellular matrix, apoptosis of endothelial cells, activation of transcription factors (NFkB, AP-1), and over-expression of inflammatory cytokines and adhesion molecules (ICAM-1, VCAM-1 , E-selectin). Recent evidences suggest that the major source of reactive oxygen species is the NADPH-oxidase, especially activated by angiotensin II, shear stress and hyperglycemia. The unbalance between production of free radicals and the ability to neutralize them by antioxidant systems causes a condition of "oxidative stress". Reactive oxygen species alter vascular tone by increasing concentration of cytosolic calcium and especially causing a decreased availability of nitric oxide, the principal agent of endothelial function with vasodilating action (Urso & Caimi, 2011).

Ischemia/reperfusion is accompanied by an increase in radical oxygen species, a situation known as oxidative stress. The superoxide anion formed reacts with nitric oxide and inactivates nitric oxide (endothelial dysfunction) producing peroxynitrite, a highly reactive oxidant specie that exerts profound deleterious effects on renal function. The amount of peroxynitrite and, thus, the severity of postischemic acute kidney injury will depend on the relative concentration of both nitric oxide and superoxide (Miles et al, 1996) in such a way that the higher the nitric oxide concentration, the lower peroxynitrite will be formed and less renal damage will take place after ischemia. Renal nitric oxide levels increase dramatically during ischemia decreasing to near preischemic levels on reperfusion (Figure 1). The increase in nitric oxide concentration seems to be independent of nitric oxide synthases and appears to originate in tissue nitric oxide stores that release nitric oxide

during ischemia (Salom et al, 2005). Combined with superoxide produced during ischemia, the nitric oxide increase appears to be responsible for an important part of the ensuing renal damage.

It has been reported that arterial ischemia produces an abrupt and significant increase in tissue nitric oxide concentration, which can last as long as ischemia is maintained and returns to preischemic levels during reperfusion. This phenomenon has been observed in kidney (Saito & Miyawaga, 2000) as well as in other organs (Lhuillier et al, 2003; Zweier et al, 1999). Although its physiological relevance is unclear, it may generate the high levels of peroxynitrite anion formed during reperfusion when a burst of superoxide anion reacts with the high levels of nitric oxide accumulated during ischemia (Miles et al, 1996), thus contributing to reperfusion damage. The mechanism responsible for these increased nitric oxide levels during renal ischemia is unknown, although it seems to be partially insensitive to nitric oxide synthesis inhibition, at least in liver and kidney (Lhuillier et al, 2003; Saito & Miyawaga, 2000). This is not surprising because nitric oxide synthase requires molecular oxygen. Therefore, during ischemia, nitric oxide must be released from other sources, such as tissue nitric oxide stores (Muller et al, 1996; Rodriguez et al, 2003; Sogo et al, 2000).

In the presence of oxygen, nitric oxide is synthesized from L-arginine through the action of nitric oxide synthase, and this gaseous hormone acts in the kidney by stimulating guanylyl cyclase and by inhibiting cytochrome *P*-450 (López et al, 2003). However, as soon as it is synthesized, nitric oxide avidly reacts with molecular oxygen, superoxide anion, and heme groups. The wide availability of these nitric oxide scavengers in all tissues argues against the simple diffusion-limited transport of free nitric oxide from synthase to cyclase or cytochrome. This implies that nitric oxide must be stabilized in vivo by reacting with carrier molecules that prolong its half-life and preserve its biological activity. This role may be subserved by biological molecules containing sulfhydryl groups that readily react with nitric oxide to form *S*-nitrosothiols (Stamler et al, 1992b), which are significantly more stable than nitric oxide itself and have been shown to be long-lasting and potent vasodilators. These compounds have been postulated to be biologically active intermediates in the mechanism of action of nitric oxide (Stamler 1992a). From this point of view, it has been shown that, at physiological concentrations, nitric oxide reacts with thiols in the presence of oxygen to form *S*-nitrosoglutathione (Kharitonov et al, 1995) and that nitric oxide circulates in mammalian plasma as nitrosothiols, mainly *S*-nitroso-serum albumin (Stamler et al, 1992a). The abundance of *S*-nitrosothiols in plasma compared with that of nitric oxide (3- to 4-fold) (Stamler et al, 1992a) suggests that plasma *S*-nitrosothiols may serve as a reservoir of nitric oxide, acting as an effective buffer (Lhuillier et al, 2003). This has also been shown in vascular tissue (Muller et al, 1996), where *S*-nitrosothiols are known to cause a prolonged nitric oxide-dependent relaxation (Sogo et al, 2000). These facts led us to hypothesize that renal ischemia induces an increase in tissue nitric oxide levels likely coming from tissue nitrosothiol stores and therefore that this phenomenon should be dependent on the presence of thiol groups in the tissue. In a study performed in our laboratories (Salom et al, 2005) we found that renal ischemia is followed by a rapid increase in intrarenal nitric oxide concentration that is maintained until reperfusion, when a fast drop in nitric oxide levels near preischemic values is observed. The increased nitric oxide concentration observed seems to be independent of nitric oxide synthase and appears to originate in tissue nitric oxide stores that release nitric oxide during ischemia.
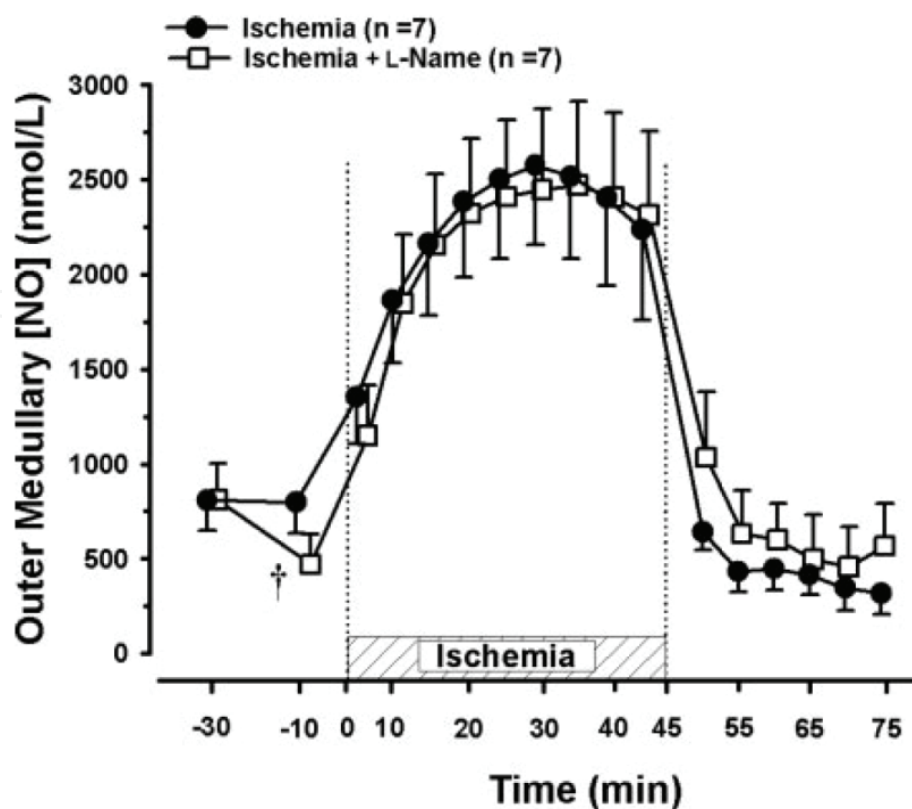
Fig. 2. Changes in nitric oxide levels in Outer Medulla during renal ischemia/reperfusion Changes in nitric oxide levels in outer medulla before, during and after a 45 min renal artery occlusion in SD rats infused with either saline (Ischemia) or L-Name (10 µg/kg/min, Ischemia + L-Name).).† Significant difference from the control period (-30 min) (Salom MG et al, 2005)

8. Sex differences in renal response to AKI

Females are known to suffer less severe renal I/R injury than males (Hutchens et al, 2008; Kang et al, 2004; Kher et al, 2005; Si et al, 2009; Wei et al, 2005; Xue et al, 2006) being the incidence of end stage renal disease approximately 50% higher in men than women. However, the mechanisms explaining this difference remain to be determined. It has been hypotethized that sex differences could be due to a higher renal constitutive nitric oxide synthase activity and/or increased nitric oxide bioavailability in females that protects the kidney against I/R injury (Chambliss & Shaul, 2002). However, lower, higher, or similar levels of endothelial and neuronal nitric oxide synthase expression in renal homogenates, cortex, and medulla of males and females have been reported (Erdely et al, 2003; Ji et al, 2005; Reckelhoff et al, 1998; Rodriguez et al, 2010; Wang et al, 2006; Wangensteen et al, 2004). However, the physiological meaning of nitric oxide synthase expression alone is uncertain, because dissociation between nitric oxide synthase expression and activity has been reported (Reckelhoff et al, 1998). The fact that nitric oxide availability depends not only on nitric oxide synthase expression and activity but also on the production of reactive oxygen species (because they inactivate nitric oxide in a concentration-dependent manner) also implies that sex differences could be due to a lower oxidative stress in females leading to increased nitric oxide levels (Arnal et al, 1996; Barbacanne et al, 1999) compared with

males (Brandes & Mügge, 1997). Thus, the reduced susceptibility of females to I/R injury may be due to a greater nitric oxide synthase activation, nitric oxide bioavailability, and/or lower free radicals formation during ischemia and early reperfusion, resulting in a less severe acute renal failure. In a recent study performed in our laboratory (Rodríguez et al 2010) we evaluated sex differences in outer medullary changes of nitric oxide and peroxynitrite levels during 45 min of ischemia and 60 min of reperfusion in SD rats. No sex differences were observed in endothelial and neuronal nitric oxide synthases nor in nitric oxide and peroxynitrite levels. We also found that a 45-min ischemia was followed after 24 h of reperfusion by a postischemic renal failure in males but not in females. This sex difference was associated with lower nitric oxide and greater peroxynitrite and 3-nitrotyrosine levels in males during ischemia, indicating increased oxidative and nitrosative stress. Pretreatment with the antioxidants N-acetyl-L-cysteine or ebselen abolished sex differences in peroxynitrite, nitrotyrosine, and glomerular filtration rate, suggesting that a greater oxidative and nitrosative stress worsens renal damage in males. Taken together, the data in the present study strongly suggest that the resistance of females to renal failure may be related to a greater renal tissular antioxidant capacity that could blunt the conversion of nitric oxide to peroxynitrite during ischemia.

9. Role of heme oxygenase system in renal I/R

Heme is a ubiquitous molecule with an active iron center with high affinity for oxygen which allows for transport of oxygen in hemoglobin and myoglobin. Heme also serves as the catalytic site in a variety of proteins involved in cell metabolism including respiratory chain cytochromes and numerous cytochrome P450 isoenzymes (Maines, 1997). Oxidative stress destabilizes heme proteins, leading to free heme release, which has prooxidant and toxic effects through free radical formation, and lipid peroxidation in renal tissues, (Akagi et al, 2002).

Intracellular free levels are tightly controlled in most cells and tissues by heme oxigenases (HO) which catalyze the initial and rate limiting step in heme catabolism (Tenhunen et al, 1968). Oxidative cleavage of heme molecules by HO yields equimolar quantities of biliverdin (BV), carbon monoxide (CO), and Fe^{+2}. Biliverdin undergoes further degradation to bilirubin (BR) by the cytosolic biliverdin reductase. All HO-derived products are biologically active substances: biliverdin and iron are believe to subserve antioxidant and prooxidant mechanisms, respectively (Abraham et al, 1997), whereas HO-derived CO exerts exerts vasorelaxant (Zhang et al, 2001), antiapoptotic, and anti-inflammatory effects.

Oxidative stress promotes the upregulation of the inducible isoform of heme oxygenase (HO-1) (Motterlini et al, 2002), which is expressed, along with the constitutive HO-2 isoform, in renal vascular and tubular structures in renal cortex and medulla (Abraham et al, 2009). HO-1 and HO-2 catalyze the same reaction and have similar cofactors requirements, but they differ with respect to the regulation and expression pattern. HO-2 accounts for the bulk of renal HO activity in normal conditions, whereas HO-1 operates as an inducible enzyme with low renal levels in the healthy kidney (Da Silva, 2001), but markedly increased in pathological conditions associated to hypoxia and inflammation (Otterbein et al, 2003).

Ischemia compromises organ function, which is further aggravated upon reperfusion, as a consequence of endothelial dysfunction, high levels of oxidative stress, altered renal

hemodynamic, and activation of the immune response. HO-1 prior to the induction of I/R results in functional protection in ischemic renal failure (Maines, 1999), which is partially mediated by reduction of oxidative and nitrosative stress during ischemia (Salom et al, 2007). Moreover, in the same way that HO metabolites maintain renal medullary perfusion (Zou et al, 2000), glomerular filtration rate and renal blood flow (Arregui B, 2004) in physiological conditions, HO-1 induction preserved postischemic medullary blood flow and GFR, in ischemic renal failure, (Salom et al, 2007). Overall, HO-1 induction might have multiple beneficial functions in I/R injury a) by reducing oxidative stress insults b) by preserving alteration of renal hemodynamic which contributes greatly to the subsequent renal failure and c) via suppression of the immune response through its anti-inflammatory actions, (Kotsch et al, 2007).

The molecular mechanisms underlying the protective role of HO induction in I/R injury are complex and likely multifactorial. Increased HO-1 activity in acute renal ischemia would result in the removal of the potent cell stressor heme (Akagi et al, 2005), but protection is also a consequence of the production of biologically active metabolites, i.e, CO, and BV. In this regard, the preadministration of exogenous CO donors in vivo have demonstrated functional protection comparable to HO-1 induction, pointing out to CO as a key component of the protection associated with HO-1 induction (Vera et al, 2005). Moreover, studies combining inhaled CO and infused bilirubin in rat renal transplantation demonstrated synergistic effects on glomerular filtration rate and renal blood flow (Nakao et al, 2005) suggesting also a role of bilirubin production in cytoprotection against ischemia/reperfusion injury. Finally, HO induction, through a variety of mechanisms, can reduce NO synthesis and, consequently, diminish augmented peroxynitrite formation during ischemia (Salom MG, 2007).

10. Concluding remarks, perspectives and significance

Ischemic injury to the renal vasculature may play an important role in the pathogenesis of both early and chronic ischemic acute kidney injury (AKI). Established and new data support the suggestion that vascular injury, in particular endothelial cell injury, participates in the extent and maintenance of AKI. Early alterations in peritubular capillary blood flow during reperfusion has been documented and associated with loss of normal endothelial cell function, which can be replaced pharmacologically or with cell replacement interventions. Distorted peritubular capillary morphology is associated with loss of barrier function that may contribute to early alterations in vascular stasis. In addition, ischemia induces alterations in endothelial cells that may promote inflammation and procoagulant activity, thus contributing to vascular congestion. Reductions in microvasculature density may play a critical part in the progression of chronic kidney disease following initial recovery from ischemia/reperfusion-induced AKI. The exact nature of how capillary loss alters renal function and predisposes renal disease is thought to be due at least in part to oxidative and nitrosative stress causing an endothelial balance between nitric oxide and peroxynitrite. Restoring the imbalance between nitric oxide and peroxynitrite will ameliorate endothelial dysfunction thus improving renal function. Finally, the loss of endothelial cell function may represent an important therapeutic target in which nitric oxide, vascular trophic support, and/or endothelial progenitor cells may show potential importance in ameliorating the acute and/or chronic effects of ischemic AKI. The use of drugs like statins that increase

hemo oxygenase-1 expression, and restores the normal imbalance beween nitric oxide and peroxynitrite (Heeba et al, 2009) and reduce postischemic renal failure (Gueler et al, 2002) seem to be promissory.

11. Grants

12. References

Abraham NG, Cao J, Sacerdoti D, Li X, Drummond G (2009). Heme oxygenase: the key to renal function regulation. *American Journal of Physiology*, 297(5):F1137-F1152

Abraham NG, Drummond GS, Lutton JD, Kappas A (1997). The biological significance and physiological role of heme oxygenase. *Cell Physiology and Biochemistry*, 247: 725,732

Akagi R, Takahashi T, & Sassa S. (2002). Fundamental role of heme oxygenase in the protection against ischemic acute renal failure. *Japanese Journal of Pharmacology*, 88: 127–132.

Akagi R, Takahashi T, Sassa S (2005). Cytoprotective effects of heme oxygenase in acute renal failure. *Contributions in Nephrology*, 148:70-85

Arnal JF, Clamens S, Pechel C, Negre-Salvayre A, Allera C, Girolami JP, Salvayre R, & Bayard F. (1996). Ethinylestradiol does not enhance the expression of nitric oxide synthase in bovine endothelial cells but increases the release of bioactive nitric oxide by inhibiting superoxide anion production. *Proceedings of the National Academy of Sciences USA* 93: 4108–4113.

Arregui B, López B, García Salom M, Valero F, Navarro C, Fenoy FJ (2004). Acute renal hemodynamic effects of dimanganese decacarbonyl and cobalt protoporphyrin. *Kidney International*, 65(2): 564-574

Baker GL, Corry RJ, & Autor AP. (1985). Oxygen free radical induced damage in kidneys subjected to warm ischemia and reperfusion. *Annals of Surgery*, 202:628-641

Barbacanne MA, Rami J, Michel JB, Souchard JP, Philippe M, Besombes JP, Bayard F, & Arnal JF. (1999). Estradiol increases rat aorta endothelium-derived relaxing factor (EDRF) activity without changes in endothelial NO synthase gene expression: possible role of decreased endothelium-derived superoxide anion production. *Cardiovascular Research* 41: 672–681

Basile DP, Donohoe DL, Roethe K, & Mattson DL. (2003). Chronic renal hypoxia after acute ischemic injury: effects of L-arginine on hypoxia and secondary damage. *American Journal of Physiology*, 284: F338-F348

Basile DP, Donohoe DL, Roethe K, & Osborn JL. (2001). Renal ischemia injury results in permanent damage to peritubular capillaries and influences long-term function. *American Journal of Physiology*, 281:F887-F899

Bird IM. (2011). Endothelial nitric oxide synthase activation and nitric oxide function: new light through old windows. Journal of Endocrinology, 210(3):239-241

Bonventre JV, & Weinberg J. (2003). Recent advances in the pathophysiology of ischemic acute renal failure. *Journal of American Society of Nephrology*, 14:2199-2210

Bonventre JV, & Zuk A. (2004). Ischemic acute renal failure: An inflammatory disease?. *Kidney International*, 66(2):480-485

Brandes RP, & Mügge A. (1997). Gender differences in the generation of superoxide anions in the rat aorta. *Life Science* 60: 391–396

Brezis M, & Rosen S. (1995). Hypoxia of the renal medulla: Its implications for disease. *New England Journal of Medicine*, 332:647-655

Brezis M, Heyman SN, Dinour D, Epstein FH, & Rosen S. (1991). Role of nitric oxide in renal medullary oxygenation. Studies in isolated and intact rat kidneys. *Journal of Clinical Investigation*, 88: 390-395

Brezis M, Rosen S, & Epstein FH. (1989). The pathophysiological implications of medullary hypoxia. *American Journal of Kidney Disease*, 13(3):253-258

Brodsky SV, Yamamoto T, Tada T, Kim B, Chen J, Kajiya F, & Goligorsky MS. (2002). Endothelial dysfunction in ischemic acute renal failure: Rescue by transplanted endothelial cells. *American Journal of Physiology*, 282: F1140–F1149

Caramelo C, Espinosa G, Manzarbeitia F, Cernadas MR, Pérez Tejerizo G, Tan D, Mosquera JR, Digiuni E, Montón M, Millás I, Hernando L, Casado S, & López-Farré A. (1996). Role of endothelium-related mechanisms in the pathophysiology of renal ischemia/reperfusión in normal rabbits. *Circulation Research*, 79:1031-1038

Chambliss KL, Shaul PW. (2002). Estrogen modulation of endothelial nitric oxide. *Endocrinology Reviews* 23: 665–686

Chatterjee PK, Cuzzocrea S, Brown PAJ, Zacharowski K, Stewart KN, Mota-Filipe H, & Thiemermann C. (2000). Tempol, a membrane-permeable radical scavenger, reduces oxidant stress-mediated renal dysfunction and injury in the rat. *Kidney International*, 58:658-673

Chatterjee PK, Nimesh SA, Patel SA, Kvale EO, Cuzzocrea S, Brown PAJ, Stewart KN, Mota-Filipe H, & Thiemermann C. (2002). Inhibition of inducible nitric oxide synthase reduces renal ischemia/reperfusion injury. *Kidney International*, 61: 862-871

Cowley AW Jr, Mori T, Mattson D, & Zou A-P. (2003). Role of renal NO production in the regulation of medullary blood flow. *American Journal of Physiology*, 284:R1355–R1369.

Cowley AW Jr. (2008). Renal medullary oxidative stress, pressure-natriuresis, and hypertension. *Hypertension*, 52:777-786

Cristol JP, Thiemermann C, Mitchell JA, Walder C, & Vane JR. (1993). Support of renal blood flow after ischemic-reperfusion injury by endogenous formation of nitric oxide and cyclo-oxygenase vasodilator metabolites. *British Journal of Pharmacology*, 109: 188-194

Da Silva, JL, Zand BA, Yang LM, Sabaawy HE, Lianos E, Abraham NG (2001). Heme oxygenase isoform-specific expression and distribution in the rat kidney. *Kidney International*, 59: 1448-1457

Devarajan P. (2006). Update on mechanism of ischemic acute kidney injury. *The Journal of the American Society of Nephrology*, 17:1503-1520

Erdely A, Greenfeld Z, Wagner L, & Baylis C. (2003). Sexual dimorphism in the aging kidney: Effects of injury and nitric oxide system. *Kidney International*, 63:1021–1026

Fenoy FJ, Ferrer P, Carbonell LF, & Salom MG. (1995).Role of nitric oxide on papillary blood flow and pressure-natriuresis. *Hypertension*, 25:408-414.

Friedewald JJ, & Rabb H. (2004). Inflammatory cells in ischemic acute renal failure. *Kidney International*, 66(2):486-491

Goligorsky MS, Brodsky SV, & Noiri E. (2004). NO bioavailability, endothelial dysfunction, and acute renal failure: new insights into pathophysiology. *Seminars in Nephrology*, 24:316-323

Gueler F, Rong S, Park JK, Fiebeler A, Menne J, Elger M, Mueller DN, Hampich F, Dechend R, Kunter U, Luft FC, & Haller H. (2002). Postischemic acute renal failure is reduced by short-term statin treatment in a rat model. *Journal of American Society of Nephrology*, 13: 2288–2298

Hansson R, Bratell S, Burian P, Bylund-Fellenius AC, Jonsson O, Lundgren O, Lunstam S, Pettersson S, & Schersten T. (1990). Renal function during reperfusion after warm ischemia in rabbits: an experimental study on the possible protective effects of pretreatment with oxygen free radical scavengers or lidoflazine. *Acta Physiologica Scandinavica*, 139;39-46

Haraldsson G, Nilsson U, Bratell S, Pettersson S, Scherstçen T, Akerlund S, & Johnsson O. (1992). ESR-measurement of production of oxygen radicals in vivo before and after renal ischaemia in the rabbit. *Acta Physiological Scandinavica*, 146(1):99-105

Heeba G, Moselhy ME, Hassan M, Khalifa M, Gryglewski R, & Malinski T. (2009). Anti-atherogenic effect of statins: role of nitric oxide, peroxynitrite and hem oxygenase-1. *British Journal of Pharmacology*, 156:1256-66

Hellberg POA, Källskog Ö, & Wolgast M. (1990b) Nephron function in the early phase of ischemic renal failure. Significance of erythrocyte trapping. *Kidney International,* 38: 432–439

Hellberg POA, Källskog Ö, Öjteg G, & Wolgast M. (1990a). Peritubular capillary permeability and intravascular RBC aggregation after ischemia: effects of neutrophils. *American Journal of Physiology*, 258: F1018–F1025

Hutchens MP, Dunlap J, Hurn PD, & Jarnberg PO. (2008). Renal ischemia: does sex matter? *Anesthesia and Analgesia*, 107: 239–249

Ignarro LJ, Byrns RE, Buga GM, Wood KS, & Chaudhuri G. (1988). Pharmacological evidence that endothelium-derived relaxing factor is nitric oxide: use of pyrogallol and superoxide dismutase to study endothelium-dependent and nitric oxide-elicited vascular smooth muscle relaxation. *The Journal of Pharmacology and Experimental Therapeutics*, 244(1):181-189

Jaimes EA, Sweeney C, & Raij L. (2001). Effects of the reactive oxygen species hydrogen peroxide and hypochlorite on endothelial nitric oxide production. *Hypertension*, 38:877-883

Jefayri MK, Grace PA, & Mathie RT. (2000). Attenuation of reperfusion-injury by renal ischaemic preconditioning: the role of nitric oxide. *British Journal of Urology International*, 85:1007-1013

Ji X, Pesce C, Zheng W, Kim J, Zhang Y, Menini S, Haywood JR, & Sandberg K. (2005). Sex differences in renal injury and nitric oxide production in renal wrap hypertension. *American Journal of Physiology* 288: H43–H47

Kadkhodaee M, Endre ZH, Towner RA, & Cross M. (1995). Hydroxyl radical generation following ischemia-reperfusion in cell-free perfused rat kidney. *Biochimica et Biophysica Acta*, 1243(2): 169-174

Kakoki M, Hirata Y, Hayakawa H, Suzuki E, Nagata D, Tojo A, Nishimatsu H, Nakanishi N, Hattori Y, Kikuchi K, Nagano T, & Omata M.. (2000). Effects of tetrahydrobiopterin

on endotelial dysfunction in rats with ischemic acute renal failure. *The Journal of the American Society of Nephrology*, 11:301-309

Kang DH, Yu ES, Yoon KI, & Johnson R. (2004). The impact of gender on progression of renal disease. Potential role of estrogen-mediated vascular endothelial growth factor regulation and vascular protection. *American Journal of Pathology,* 164: 679–688

Kharitonov VG, Sundquist AR, & Sharma VS. (1995). Kinetics of nitrosation of thiols by nitric oxide in the presence of oxygen. *Journal of Biological Chemistry*, 270: 28158–28164.

Kher A, Meldrum KK, Wang M, Tsaia BM, Pitchera JM, & Meldruma DR. (2005). Cellular and molecular mechanisms of sex differences in renal ischemia-reperfusion injury. *Cardiovascular Research,* 67: 594–603

Knight S, & Johns EJ. (2005). Effect of COX inhibitors and NO on renal hemodynamics following ischemia-reperfusion injury in normotensive and hypertensive rats. *American Journal of Physiology*, 289:F1072-F1077

Kotsch K, Martins PN, Klemz R, Janssen U, Gerstmayer B, Dernier A, Reutzel-Selke A, Kuckelkorn U, Tullius SG, Volk HD(2007). Heme oxygenase-1 ameliorates ischemia/reperfusion injury by targeting dendritic cell maturation and migration. *Antioxidant Redox Signaling*, 9(12):2049-2063

Lefer AM, & Ma X-L. (1991). Endothelial dysfunction in splanchnic circulation following ischemia and reperfusion. *Journal of Cardiovascular Pharmacology,* 17(Suppl 3):S186-S190

Legrand M, Almac E, Milk eg, Johannes T, Kandil A, Bezemer R, Payen D, & Ince C. (2009). L-NIL prevents renal microvascular hypoxia and increase of renal oxygen consumption after ischemia-reperfusion in rats. *American Journal of Physiology*, 296:F1109-F1117

Lhuillier F, Parmentier P, Goudable J, Crova P, Delafosse B, Annat G, Cespuglio R, & Viale JP. (2003). Hepatic ischemia is associated with an increase in liver parenchyma nitric oxide that is in part enzyme-independent. *Anaesthesiology* 98: 373–378

Lieberthal W, Wolf EF, Rennke HG, Valeri CR, & Levinsky NG. (1989). Renal ischemia and reperfusion impair endothelium-dependent vascular relaxation. *American Journal of Physiology*, 256:F894-F900

Lopez B, Salom MG, Arregui B, Valero F, & Fenoy FJ. (2003). Role of superoxide in modulating the renal effects of angiotensin II. *Hypertension*, 42: 1150–6.

López Conesa E, Valero F, Nadal JC, Fenoy F, López B, Arregui B, & Salom MG. (2001). N-acetyl-L-cysteine improves renal medullary hypoperfusion in acute renal failure. *American Journal of Physiology*, 281:R730-R737

Lopez-Neblina F, Toledo-Pereyra LH, Mirmiran R, & Paez-Rollys AJ. (1996). Time dependence of Na-nitroprusside administration in the prevention of neutrophil infiltration in the rat ischemic kidney. *Transplantation*, 61(2):179-183

Maines MD (1997). The heme oxygenase system: a regulator of second messenger gases. *Annual Review of Pharmacology and Toxicology*, 37: 517-554

Maines MD, Raju VS, & Panahian N. (1999). Spin trap (*N-t*-butyl-_-phenylnitrone)-mediated suprainduction of heme oxygenase-1 in kidney ischemia/reperfusion model: role of the oxygenase in protection against oxidative injury. *Journal of Pharmacology and Experimental Therapeutics,* 291: 911–919

Majid DSA, & Nishiyama A. (2002). Nitric oxide blockade enhances renal reponses to superoxide dismutase inhibition in dogs. *Hypertension,* 39:293–297.

Majid DSA, Nishiyama A, Jackson KE, & Castillo A. (2004). Inhibition of nitric oxide synthase enhances superoxide activity in canine kidney. *American Journal of Physiology,* 287: R27–R32

Majid DSA, Nishiyama A, Jackson KE, & Castillo A. (2005). Superoxide scavenging attenuates renal responses to ANG II during nitric oxide synthase inhibition in anesthetized dogs. *American Journal of Physiology,* 288: F412–F419

Makino A, Skelton MM, Zou AP, Roman RJ, & Cowley Jr AW. (2002). Increased renal medullary oxidative stress produces hypertension. *Hypertension* 39: 667–672.

Mason J, Thorhorst J, & Welsch J. (1984). Role of medullary perfusion defect in the pathogenesis of ischemic renal failure. *Kidney International,* 24: 27–36

Michel T, & Vanhoutte PM. (2010). Cell signaling and NO production. *European Journal of Physiology,* 459:

Miles AM, Scott Bolhle D, Glassbrenner PA, Hansert B, Wink DA & Grisham MB. (1996). Modulation of superoxide-dependent oxidation and hydroxylation reactions by nitric oxide. *Journal of Biological Chemistry,* 271: 40-47

Motterlini R, Green CJ, Foresti R (2002). Regulation of heme oxygenase-1 by redox signals involving nitric oxide. *Antioxidant and Redox Signaling,* 4(4):615-624

Muller B, Kleschyov AL, & Stoclet JC. (1996). Evidence for *N*-acetylcysteinesensitive nitric oxide storage as dinitrosyl-iron complexes in lipopolysaccharide-treated rat aorta. *British Journal of Pharmacology,* 119: 1281–1285

Nakajima A, Ueda K, Takaoka M, Yoshimi Y, & Matsumura Y. (2006). Opposite effects of pre- and postischemic treatments with nitric oxide dono ron ischemia/reperfusión-induced renal injury. *The Journal of Pharmacology and Experimental Therapeutics,* 316: 1038-1046

Nakanishi K, Mattson DL, & Cowley AW Jr. (1995). Role of renal medullary blood flow in the development of L-Name hypertension in rats. *American Journal of Physiology,* 268:R317-R323

Nakao A, Neto JS, Kanno S, Stolz DB, Kimizuka K, Liu F, Bach FH, Billiar TR, Choi AM, Otterbein LE, Murase N (2005). Protection against ischemia/reperfusion injury in cardiac and renal transplantation with carbon monoxide, biliverdin and both. *American Journal of Transplant,* 5(2):282-291

Nilsson UA, Haraldsson G, Bratell S, Sorensen V, Akerlund A, Pettersonn S, Schersten T, & Jonsson O. (1993). ESR-measurement of oxygen radicals in vivo after renal ischemia of the rabbit. Effect of pretreatment with superoxide dismutase and heparin. *Acta Physiologica Scandinavica,* 147:263-279

Nitescu N, Grimberg E, Ricksten S-E, & Guron G. (2006). Effects of N-acetyl-Lcysteine on renal haemodynamics and function in early ischaemi-reperfusion injury in rats. *Clinical and Experimental Pharmacology and Physiology,* 33:53-57

Nitescu N, Ricksten SE, Marcussen N, Haraldsson B, Nilsson U, Basu S, Guron G. (2006). N-acetylcysteine attenuates kidney injury in rats subjected to renal ischaemia-reperfusion. *Nephrology and Dialysis Transplantation,* 21(5):1240-7

Noiri E, Nakao A, Uchida K, Tsukahara H, Ohno M, Fujita T, Brodsky S, & Goligorsky MS. (2001). Oxidative and nitrosative stress in acute renal ischemia. *American Journal of Physiology,* 281:F948-F957

Noiri E, Peresleni T, Miller F, & Goligorsky MS. (1996). In vivo targeting of inducible NO synthase with oligodeoxynucleotides protects rat kidney against ischemia. *Journal of Clinical Investigation*, 97(10): 2377-2383

O´Connor PM, Kett MM, Anderson WP, & Evans RG, (2006). Renal medullary tissue oxygenation is dependent on both cortical and medullary blood flow. *American Journal of Physiology*, 290: F688-F694

Olof P, Hellberg A, Källskog O, & Wolgast M.(1991). Red cell trapping and postischemic renal blood flow. Differences between the cortex, outer and inner medulla. *Kidney Intrnational*, 40(4):625-631.

Otterbein LE, Soares MP, Yamashita K, Bach FH (2003*). Heme oxygenase-1: unleashing the protective properties of heme. Trends in Immunology*, 24(8):449-455

Paller MS, & Neumann TV. (1991). Reactive oxygen species and rat renal epithelial cells during hypoxia and reoxygenation. *Kidney International*, 40(6):1041-1049

Park KM, Byun J-Y, Kramers C, Kim JI, Huang PL, & Bonventre JV. (2003). Inducible nitric oxide synthase is an important contributor to prolonged protective effects of ischemic preconditioning in the mouse kidney. *The Journal of the Biological Chemistry*, 278(29):27256-27266

Park KM, Chen A, & Bonventre JV. (2001). Prevention of kidney ischemia/reperfusion-induced functional injury and JNK, p38, and MAPK kinase activation by remote ischemic pretreatment. *Journal of Biology and Chemistry,*276(15):11870-11876

Park KM, Kramers C, Vayssier-Taussat M, Chen A, & Bonventre JV. (2002). Prevention of kidney ischemia/reperfusion-induced functional injury, MAPK and MAPK kinase activation, and inflammation by remote transient ureteral obstruction. *Journal of Biology and Chemistry,*277(3):2040-2049

Pfeilschifter J, Eberhardt W, & Huwiler A. (2003). Nitric oxide and mechanisms of redox signaling. *Journal of the American Society of Nephrology*, 14:S237-S240

Polytarchou C, & Papadimitriou E. (2005).Antioxidants inhibit human endothelial cell functions through down-regulation of endothelial nitric oxide synthase activity. *European Journal of Pharmacology*, 510(1-2):31-38

Rabelink TJ, & van Zonneveld AJ. (2006) Coupling eNOS uncoupling to the innate immune response. *Arteriosclerosis, Thrombosis, and Vascular Biolology*, 26:2585–2587

Rafikov R, Fonseca FV, Kumar S, Pardo D, Darragh C, Elms S, Fulton D, & Black SM. (2011). eNOS activation and NO function: Structural motifs responsible for the posttranslational control of endothelial nitric oxide synthase activity. *Journal of Endocrinology*, 210:271-284

Reckelhoff JF, Hennington BS, Moore AG, Blanchard EJ, & Cameron J. (1998). Gender differences in the renal nitric oxide (NO) system: dissociation between expression of endothelial NO synthase and renal hemodynamic response to nitric oxide inhibition. *American Journal of Hypertension,* 11: 97–104

Rodríguez F, Nieto-Cerón S, Fenoy FJ, López B, Hernández I, Rodado Martinez R, González Soriano MJ, & Salom MG. (2010). Sex differences in nitrosative stress during renal ischemia. *American Journal of Physiology*, 299: R1387–R1395

Rodriguez J, Maloney RE, Rassaf T, Bryan NS, & Feelisch M. (2003) Chemical nature of nitric oxide storage forms in rat vascular tissue. *Proceedings of the National Academy of Sciences, USA* 100: 336–341

Romero JC, Lahera V, Salom MG, & Biondi LM. (1992). Role of the endothelium-dependent relaxing factor Nitric Oxide on renal function. *Journal of the American Society of Nephrology*, 2: 1371-1387

Rosenberger C, Mandriota S, Jürgensen JS, Wiesener MS, Hörstrup JH, Frei U, Ratcliffe PJ, Maxwell PH, Bachmann S, & Eckardt K-U. (2002). Expression of Hypoxia-Inducible Factor-1α and -2α in Hypoxic and Ischemic Rat Kidneys. *Journal of the American Society of Nephrology*, 13: 1721–1732

Rosenberger C, Rosen S, & Heyman SN. (2006). Renal parenchymal oxygenation and hypoxia adaptation in acute kidney injury. *Clinical and Experimental Pharmacology and Physiology,* 33(10):980-988

Saito M, & Miyagawa I. (2000). Real-time monitoring of nitric oxide in ischemia-reperfusion rat kidney. *Urology Research,* 28: 141–146

Salom MG, Arregui B, Carbonell LF, Ruiz F, González-Mora JL, & Fenoy FJ. (2005). Renal ischemia induces an increase in nitric oxide levels from tissue stores. *American Journal of Physiology*, 289: R1459–R1466

Salom MG, Nieto-Cerón S, Rodríguez F, López B, Hernández I, Gil J, Martínez-Losa A, & Fenoy FJ. (2007). Heme-oxygenase-1 induction improves ischemic renal failure. Role of nitric oxide and peroxynitrite. *American Journal of Physiology*, 293: H3542–H3549

Salom MG, Ramírez P, Carbonell LF, López Conesa E, Cartagena J, Quesada T, Parrilla P, & Fenoy FJ. (1998). Protective effect of N-acetyl-L-cysteine on the renal failure induced by inferior vena cava occlusion. *Transplantation*, 65:1315-1321

Schrier RW, Wang W, Poole B, & Mitra A. (2004). Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. *The Journal of Clinical Investigations*, 114(1):5-14

Si H, Banga RS, Kapitsinou P, Ramaiah M, Lawrence J, Kambhampati G, Gruenwald A, Bottinger E, Glicklich D, Tellis V, Greenstein S, Thomas DB, Pullman J, Fazzari M, & Susztak K. (2009). Human and murine kidneys show gender- and species-specific gene expression differences in response to injury. *PLoS One*, 4(3):e4802. Epub 2009

Sogo N, Campanella C, Webb DJ, & Megson IL. (2000). *S*-nitrosothiols cause prolonged, nitric oxide-mediated relaxation in human saphenous vein and internal mammary artery: therapeutic potential in bypass surgery. *British Journal of Pharmacology,* 131: 1236–1244

Solez K, Kramer EC, Fox JA, Heptinstall RH. (1974). Medullary plasma flow and intravascular leukocyte accumulation in acute renal failure. *Kidney International,* 6(1):24-37

Stamler JS, Jaraki O, Osborne J, Simon DI, Keaney J, Vita J, Singel D, Valeri CR, & Loscalzo J. (1992a). Nitric oxide circulates in mammalian plasma primarily as an S-nitroso adduct of serum albumin. *Proceedings of the Nationall Academy of Sciences, USA*, 89: 7674–7677

Stamler JS, Simon DI, Osborne JA, Mullins ME, Jaraki O, Michel T, Singel DJ, & Loscalzo J. (1992b) *S*-nitrosylation of proteins with nitric oxide: synthesis and characterization of biologically active compounds. *Proceedings of the Nationall Academy of Sciences USA* 89: 444–448

Stuehr DJ. (1997). Structure–function aspects in the nitric oxide synthases. *Annual Review of Pharmacology and Toxicology*, 37: 339–359

Summers W, & Jamison RL. (1971). The non-reflow phenomenon in renal ischemia. *Laboratory Investigation*, 25:635-643

Sutton TA, Fisher CJ, & Molitoris BA.(2002). Microvascular endothelial injury and dysfunction during ischemic acute renal failure. *Kidney International,* 62(5):1539-1549

Tenhunen R, Marver HS, Schmid R (1968). The enzymatic conversion of heme to bilirubin by microsomal heme oxygenase. *Proceedings of the National Academy of Sciences, U S A.,* 61(2):748-755

Torras J, Herrero-Fresneda I, Lloberas N, Riera M, Cruzado JMª, & Grinyó JMª. (2002). Promising effects of ischemic preconditioning in renal transplantation. *Kidney International*, 61:2218-2227

Tsao PS, & Lefer AM. (1990). Time course and mechanism of endothelial dysfunction in isolated ischemic and hypoxic perfused rat hearts. *American Journal of Physiology*, 259:H1660-H1666

Tsao PS, Aoki N, Lefer DJ, Johnson G III, & Lefer AM. (1990). Time course of endothelial dysfunction and myocardial injury during myocardial ischemia and reperfusion in the cat. *Circulation*, 82:1402-1412

Tsuji T, Kato A, Yasuda H, Miyaji T, Luo J, Sakao Y, Ito H, Fujigaki Y, & Hishida A. (2009). The dimethylthiourea-induced attenuation of cisplatin nephrotoxicity is associated with the augmented induction of heat shock proteins. *Toxicology and Applied Pharmacology,* 234(2):202-208

Urso C, & Caimi G. (2011). Oxidative stress and endothelial dysfunction. *Minerva Medical*, 102(1):59-77

Vera T, Henegar JR, Drummond HA, Rimoldi JM, & Stec DE. (2005). Protective effect of carbon monoxide-releasing compounds in ischemia-induced acute renal failure. *Journal of the American Society of Nephrology,* 16(4):950-958

Walker LM, Walker PD, Imam SZ, Ali SF, & Mayeux PR. (2000). Evidence for peroxynitrite formation in renal ischemia-reperfusion injury: Studies with the inducible Nitric Oxide Synthase inhibitor L-N^6-(1-iminoethyl)lysine. *Journal of Pharmacology and Experimental Therapeutics*, 295:4177-22

Walker LM, York JL, Imam SZ, Ali SF, Muldrew KL, & Mayeux PR. (2001). Oxidative stress and reactive nitrogen species generation during renal ischemia. *Toxicological Sciences*, 63: 143-148

Wang X, Desai K, Juurlink BHJ, de Champlain J, & Wu L. (2006). Gender-related differences in advanced glycation endproducts, oxidative stress markers and nitric oxide synthases in rats. *Kidney International*, 69: 281–287

Wangensteen R, Moreno JM, Sainz J, Rodríguez-Gómez I, ChamorroV, Luna de D J, Osuna A, & Vargas F. (2004). Gender difference in the role of endothelium-derived relaxing factors modulating renal vascular reactivity. *European Journal of Pharmacology,* 486: 281–288

Wei Q, Wang MH, & Dong Z. (2005). Differential gender differences in ischemic and nephrotoxic acute renal failure. *American Journal of Nephrology*, 25: 491–499

Wu F, Park F, Cowley AW Jr, & Mattson DL. (1999). Quantification of nitric oxide synthase activity in microdissected segments of the rat kidney. *American Journal of Physiology,* 276: F874–F881

Yamamoto T, Tada T, Brodsky SV, Tanaka H, Noiri E, Kajiya F, & Goligorsky MS. (2002). Intravital videomicroscopy of peritubular capillaries in renal ischemia. *American Journal of Physiology*, 282: F1150–F1155

Yamasowa H, Shimizu S, Inoue T, Takaoka M & Matsumura Y. (2005). Endothelial nitric oxide contributes to the renal protective effects of ischemic preconditioning. *The Journal of Pharmacology and Experimental Therapeutics*, 312: 153-159

Zhang F, Kaide JI, Rodriguez-Mulero F, Abraham NG, Nasjletti A (2001). Vasoregulatory function of the heme-heme oxygenase-carbon monoxide system. *American Journal of Hypertension:* 14(6 Pt 2):62S-67S

Zhang W, & Edwards A. (2002). Oxygen transport across vasa recta in the renal medulla. *American Journal of Physiology*, 283:H1042-H1055

Zhang W, Pibulsonggram, & Edwards A. (2004). Determinants of basal nitric oxide concentration in the renal medullary microcirculation. *American Journal of Physiology*, 287:F1189-F1203

Zhang ZG, Chopp M, Bailey F, and Malinski T. Nitric oxide changes in the rat brain after transient middle cerebral artery occlusion. *Journal of Neurology Sciences,* 128: 22–27, 1995.

Zou A-P, & Cowley AW Jr. (1997). Nitric oxide in renal cortex and medulla: an in vivo microdialysis study. *Hypertension*, 29:194-198

Zou AP, & Cowley Jr AW. (2001). Production and actions of superoxide in the renal medulla. *Hypertension,* 37: 547–553.

Zou, AP, Billington H, Su N, & Cowley AW, Jr. (2000). Expression and actions of heme oxygenase in the renal medulla of rats. *Hypertension,* 35:342-347
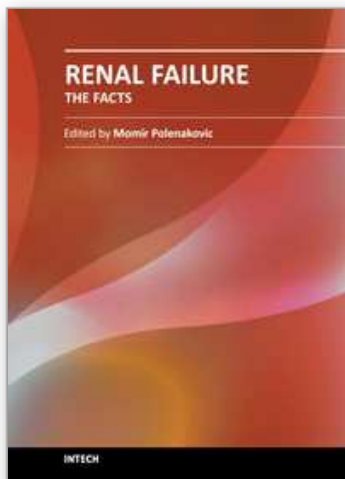
Renal Failure - The Facts

Edited by Dr. Momir Polenakovic

The book "Renal Failure - The Facts" consists of some facts about diagnosis, etiopathogenis and treatment of acute and chronic renal failure. Acute, as well as chronic renal failure is great medical problems and their treatment is a burden for the budget of each government. The purpose of the chapters is to present some important issues of diagnosis and causes of AKI, as well as caused by snakes and arthropods, after cardiac surgery, as well as some therapeutic achievements in AKI. Well presented are the psychological condition in patients on haemodialysis, as well as the treatment of diabetic uremics. The book is aimed at clinicians with a special interest in nephrology, but it should also prove to be a valuable resource for any generalists who encounter a nephrological problems in their day-to-day practice.

How to reference

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Miguel G. Salom, B. Bonacasa, F. Rodriguez and F. J. Fenoy (2012). Oxidative and Nitrosative Stress in the Ischemic Acute Renal Failure, Renal Failure - The Facts, Dr. Momir Polenakovic (Ed.), ISBN: 978-953-51-0630-2, InTech, Available from: http://www.intechopen.com/books/renal-failure-the-facts/oxidative-and-nitrosative-stress-in-the-ischemic-acute-renal-failure

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