Chapter 2
ROS in Atherosclerotic Renovascular Disease

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Introduction

Atherosclerotic renovascular disease (ARVD) is a major cause of secondary hypertension, especially in the elderly population. ARVD typically involves the proximal third of the renal artery including the perirenal aorta and ostium. The prevalence of ARVD is about 6.3–6.8 % in patients undergoing angiography or as determined in a population-based study utilizing a noninvasive screening technique [1, 2], and is increased in elderly patients with additional comorbid conditions such as diabetes, hypertension, or coronary artery disease [3]. ARVD is a progressive disease in regards to both the lesion severity and kidney function, and might confer a poor prognosis to affected patients.

The relationship between unilateral renal artery stenosis and arterial hypertension has been demonstrated in the original experiments of Goldblatt et al. [4], which led to the discovery of renin-angiotensin-aldosterone system (RAAS). Furthermore, because of the reduced perfusion beyond the stenosis, the tissue of the stenotic kidney is exposed to chronic hypoxia, which leads to ischemic kidney disease. In the contralateral kidney however, renal damage progressively develops by the hypertension caused by activation of the RAAS and volume overload.

We have previously shown in our animal model an early increase in systemic plasma renin activity (PRA, 4-5 weeks after induction of renal artery stenosis), as seen in the early phases of renovascular hypertension [5, 6], returns to baseline by 8 weeks. Few data track PRA over time in ARVD patients, but it seems to also show an early increase and later normalize [7]. These data indicate that hypertension in

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the late phase of ARVD may be maintained by other mechanisms. We have shown [8] that increased oxidative stress and upregulation of inflammatory factors in ARVD are associated with marked impairments of renal hemodynamics and function and that increased abundance of reactive oxygen species (ROS) initially leads to renal microvascular endothelial dysfunction, which may precede and subsequently be aggravated by the development of obstructive lesions in the main renal artery. In a murine model of renovascular hypertension [9], up regulation of both pro- and anti-oxidant genes were observed as early as 3 days after renal artery stenosis before the renal tissue demonstrates any histologic abnormalities. Oxidative stress is defined as a tissue injury induced by increase in ROS such as oxygen radicals, which can be generated at different sites along the nephron, like the glomeruli and segments two and three of the proximal tubule. ARVD is associated with activation of oxidative pathways, reduction in nitric oxide (NO) synthesis and stimulation of the RAAS, in both human subjects and experimental models (Fig. 2.1). The goal of this chapter is to review the potential role of ROS in ARVD.

Mechanisms of ROS Generation in the Stenotic Kidney

RAAS Activation

More than one century ago, Tigerstedt and Bergman introduced the concept that "renin" in the kidney may have a systemic pressor effect [10]. In the 1930s, Goldblatt et al. [4] demonstrated that uni- or bilateral clip of the renal artery cause blood pressure rise and attributed the pressor effect to "internal secretion" of the kidney that triggers vasoconstriction. Renin was subsequently successfully isolated by Braun-Menendez and Irvine Page [11], but renin itself has little vasopressor activity. Skeggs and colleagues [12] characterized the hormonal cascade downstream to renin, including angiotensin-I (Ang I), angiotensin converting enzyme (ACE), and angiotensin-II (Ang II). Kidney juxtaglomerular (JG) cells secrete renin, which converts angiotensinogen (the main source of which is the liver) to Ang I. Ang I is cleaved by ACE originating from the lung and kidney to Ang II, which elevates blood pressure by several mechanisms. Ang II activates sympathetic nerve activity and induces arteriolar vasoconstriction, but also increases sodium and water retention by tubular reabsorption, which is accelerated by aldosterone secreted by the adrenal gland. Furthermore, Ang II stimulates anti-diuretic hormone secretion in the pituitary gland, leading to increased water reabsorption in the collecting duct [13]. Those systemic effects of Ang II increase water and sodium retention and the effective circulating volume, resulting in increased perfusion pressure at the JG apparatus, leading to decreased renin secretion by negative feedback. Therefore, the decrease in renal perfusion pressure induced by the vascular occlusion in ARVD stimulates JG cells to secrete renin and thereby activates the cascade of RAAS resulting in renovascular hypertension.

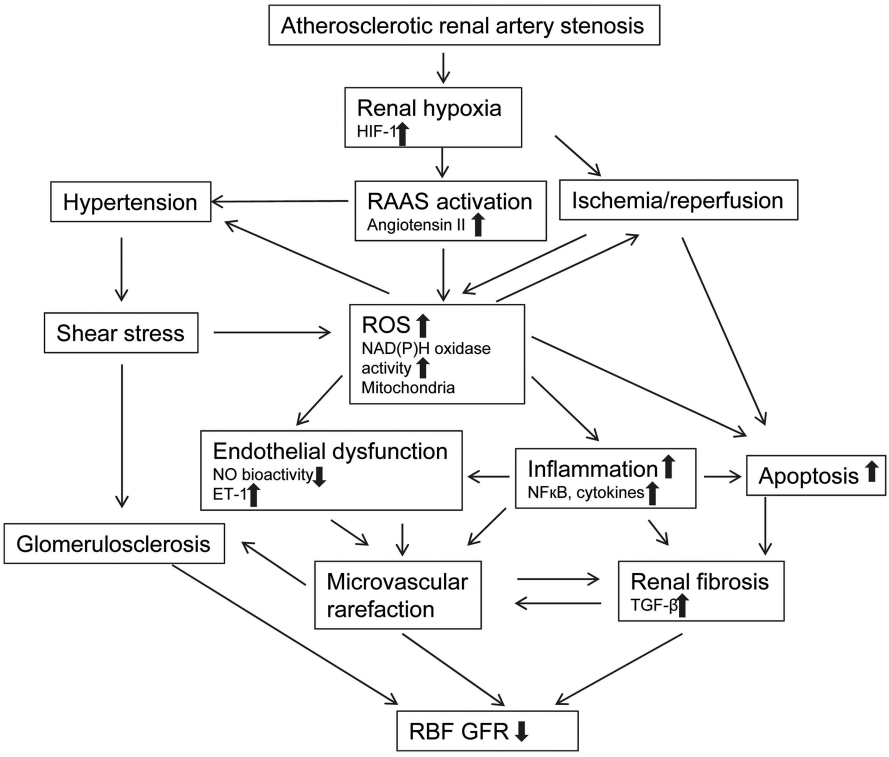

Fig. 2.1 Overview of the role of reactive oxygen species (ROS) in the mechanisms of atherosclerotic renovascular disease (ARVD). In ARVD, renal ischemia induces tissue hypoxia and hypoxia inducible factor (HIF)-1 upregulation. Hypoxia activates renin-angiotensin-aldosterone system (RAAS). Angiotensin II mainly stimulate nicotinamide adenine dinucleotide phosphate (NAD(P)H)-oxidase to generate ROS, which decrease nitric oxide (NO) bioactivity and induce endothelial dysfunction. Angiotensin II also induces inflammatory factors and cytokines such as nuclear factor kappa B (NFκB) and transforming growth factor (TGF)-β, and cell apoptosis, subsequently lead to microvascular rarefaction and renal fibrosis. Furthermore, angiotensin II, ROS, and inflammation impair tubular function, lead water sodium retention elevate blood pressure. Hypertension-induced shear stress can also induce ROS impair endothelial function and cause glomerulosclerosis. These entire cascades together decrease renal blood flow (RBF) and glomerular filtration rate (GFR)

In addition to systemic RAAS, all the elements of RAAS have been discovered and can be produced in the kidney [14]. Renin is secreted from JG cells, the collecting duct, and collecting duct. Intrarenal angiotensinogen is produced mainly in the proximal tubule and ACE in the proximal tubule, the collecting duct, and endothelial cells. Furthermore, intrarenal formation of Ang II is independent of the circulating RAAS. The concentration of intrarenal Ang II is much higher than systemic level. In an early phase of renal artery stenosis, the JG cellular renin is increased in the stenotic kidney. After the acute stage, JG renin is suppressed by negative feedback, upregulated renin is produced in the distal nephron and in the collecting duct in the contralateral kidney to support continued intrarenal Ang II formation leading

to maintenance of hypertension. Furthermore, Ang II activates proximal tubular secretion of ACE and ACE binding activity [15].

Ang II-induced activation of nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase leads to increased production of ROS. Ang II simulated mitochondrial NAD(P)H oxidase isoform 4 and resulted in the abrupt production of mitochondrial superoxide and hydrogen peroxide (H_2O_2). Ang II also induced depolarization of the mitochondrial membrane potential, and cytosolic secretion of cytochrome C and apoptosis-inducing factor [16] (Fig. 2.1).

Elevated ROS produce an oxidized form of angiotensinogen with greater potency to bind renin, facilitates angiotensin release, and increase blood pressure [17]. Since ROS are extracellular signaling molecules, they may be significant in mediating the actions of vasoconstrictors, such as Ang II, thromboxane A2, endothelin-1, adenosine, and norepinephrine. Thus, the activation RAAS starts the entire ROS-dependent cascades in ARVD.

Inflammation

The activation of the RAAS leads to production of Ang II, which can induce oxidative stress by upregulating NAD(P)H oxidase, impairs endothelial function, and increases vascular permeability, subsequently increase macrophage infiltration [18], possibly by upregulation of monocyte chemoattractant protein-1 (MCP-1), a chemokine that increases monocyte infiltration into inflamed tissues and an important inflammatory mediator. In mice ischemia/reperfusion (I/R) model, there was a large influx of inflamed monocytes into the kidney. These monocytes produced tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-1α, and IL-12 [19]. Activated macrophages and fibroblasts in the ARVD kidney may again directly induce NAD(P)H oxidase activity, stimulating transforming growth factor (TGF)-β1 production and triggering fibroblast proliferation and differentiation into collagen-secreting myofibroblasts [20]. Neutralization of MCP-1 reduces macrophage infiltration and progressive kidney damage in rat tubulointerstitial nephritis [21]. Acute infusion with Ang II significantly increases leukocytes adhesion in the rat mesenteric arteries and increased expression of vascular cell adhesion molecule (VCAM)-1 in rat aorta via nuclear factor kappa-B (NF-κB) transcriptional activation [22], which can be inhibited by administration of losartan, an Ang II type I Receptors (AT1R) antagonist. Studies show that Ang II elicits proinflammatory responses in the kidney by regulating the expression of cytokines and chemokines [23]. Ang II induces NF-κB activation and the expression of IL-6 in human vascular smooth muscle cells [24]. Ang II also play a significant role in the initiation and progression of atherogenesis [25], an inflammation mediated process, where Ang II provides a positive feedback loop in vascular inflammation via recruitment of inflammatory cells, which then induce production of more Ang II, therefore perpetuating vascular inflammation. Moreover, inflammatory factors like TNF-α can also induce ROS that serve as second messengers for intracellular signaling, in mesangial cells, TNF-α induces apoptosis through superoxide anion, but not H_2O_2 [26].

The proinflammatory effects of the RAAS are partly mediated by aldosterone. Aldosterone promotes insulin resistance and vascular remodeling and influences the development of atherosclerosis. Chronic infusion of aldosterone induces oxidative stress in rat aorta, and MR antagonist spironolactone reduces ROS generation. Human and rat adrenal cortical cells stimulated with Ang II produce aldosterone via AT1R-upregulation of cytochrome P450 oxidase B2 and increased level of hydrogen peroxide, whereas pretreatment with losartan and antioxidants abrogates Ang II effects [27].

These studies suggest the interaction between ROS and inflammation in the kidney injury in ARVD.

Comorbidities

Coexistence of hypercholesterolemia aggravates the effects of renal artery stenosis on both vascular and kidney injury. For example, unilateral renal artery narrowing in ApoE/mice results in chronic vascular inflammation and accelerated atherosclerosis compared to sham-surgery [28]. The atheroma is cellular in composition and stains for the presence of macrophages and MCP-1 in both the distal abdominal aorta and carotid artery [28].

Furthermore, our previous study [8] demonstrated that the combination of hypercholesterolemia and renal artery stenosis amplifies activation of mechanisms that can promote renal vascular, glomerular, and tubulointerstitial injury compared with renal artery stenosis alone. Hypercholesterolemia and renal artery stenosis were associated with a marked increase in tubular and glomerular expression of profibrotic TGF-β, tissue inhibitor of matrix metalloproteinase (TIMP)-1, and (plasminogen activator inhibitor (PAI)-1, accompanied by increased expression of NF-κB, but attenuated the expression of MMP-2 and ubiquitin, and decreased apoptosis compared with ARVD, suggesting a shift in the tissue remodeling process that favors renal fibrosis and matrix accumulation.

Diabetes is a common risk factor that often coexists with ARVD. Increased oxidative stress, formation of advanced glycoxidation end products (AGEs), chronic inflammation, and activated cellular response are the major molecular mechanisms of atherogenesis in diabetic patients. Furthermore, elevated free fatty acids, high glucose levels, or AGEs induce ROS in vascular cells, leading to ongoing AGE formation and to generation of proinflammatory cytokines [29]. Moreover, elevated cytokines in obesity and diabetes may also induce oxidative stress thus a vicious cycle may be initiated and accelerated. Increased ROS may upregulate NF-κB expression through protein kinase C and the mitogen-activated protein kinase pathway, and subsequently induce the expression of numerous cytokines which act on vascular cells promoting the deleterious effects [30]. Studies have demonstrated that the NAD (P)H oxidase and the AGE/RAGE/NF-κB axis accelerated atherosclerosis [31]. The blockade of ROS or AGE formation at different sites may interrupt the vicious cycle, e.g. ACE

inhibitors, AT1 receptor blockers, 3-hydroxy-3- methyl-glutaryl-CoA reductase inhibitors (statins), and thiazolidindiones have shown intracellular antioxidant activity in addition to their primary pharmacological actions.

Elements of Ischemia-Reperfusion Injury

Kidney ischemia-reperfusion (I/R) injury (IRI) is often observed in acute kidney injury, which impairs renal function through different cascades of ROS and inflammation compared with chronic ARVD (Fig. 2.2). However, it may also occur in ARVD due to cholesterol emboli or rupture of an atherosclerotic lesion causing an

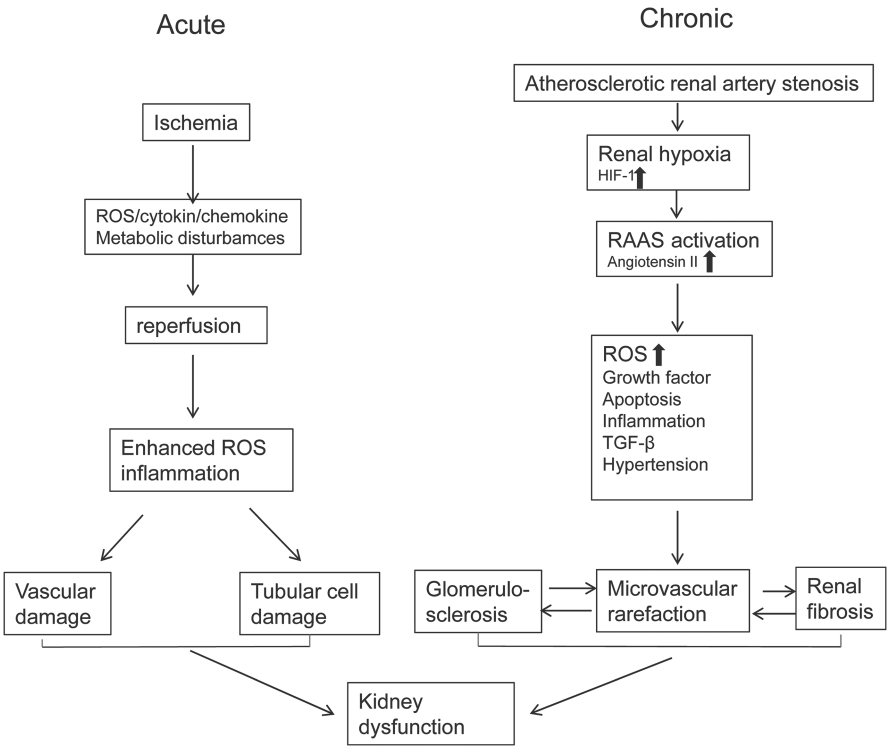

Fig. 2.2 Acute vs. chronic modulation of renal function in atherosclerotic renovascular disease (ARVD). In acute renal ischemia, interruption of kidney perfusion results in a rapid drop in oxygen and nutrient supply, which leads to hypoxic damage and ROS formation. Reperfusion induces a massive and local production of ROS and inflammatory factors, which are responsible for vascular and tubular cell damage. In chronic ARVD, the mechanisms are series cascades of activation renin-angiotensin-aldosterone system (RAAS), including ROS, inflammation apoptosis and growth factor degrading, eventually lead to glomerulosclerosis, microvascular rarefaction, and renal fibrosis

in site thrombosis. Initially, a sustained interruption of kidney perfusion results in a rapid drop in oxygen and nutrient supply, which leads to hypoxic damage. Hypoxia causes a rapid depletion of the energy supply, intracellular accumulation of lactate, and acidification of cell cytosol. In addition, the lack of energy delivery induces disorganization of the cytoskeleton, disruption of intercellular tight junctions, loss of cell polarity, and dysfunction of membrane ion transporters. Consequently, epithelial and endothelial cells detach from their basal membrane and obstruct tubular and vascular lumens. The loss of tubular and vascular select-permeability eventuates accumulation of fluids in the interstitium, which further delays kidney reperfusion and prolongs the ischemic insult. Ischemia also induced ROS which cause cellular injury. However, abrupt reperfusion also induces a massive and local production of ROS, which are responsible for detrimental oxidation of proteins, lipids, membranes, and nucleic acids of both epithelial and endothelial cells, leads to pronounced tissue damage [32]. In addition to all these metabolic consequences, inflammatory reaction characterized by the expression and activation of endothelial adhesion molecules, integrins, and selectins also participate the processing of IRI [33]. These inflammatory molecules in turn activate the innate immune responses via the Toll-like receptors, and recruit inflammatory cells [34]. The deleterious impact of I/R-associated inflammation and infiltration of monocytes involves chemokine receptors, such as chemokine receptor-2, chemokine receptor-7, and CXC chemokine receptor-4, as well as the local production of ROS, TNF-α, and IL-1β [35].

Recent studies demonstrate that microRNAs, which are short endogenous non-coding RNAs, are important regulators of target messenger RNAs involved in IRI. Dicer cleaves pre-microRNA into short microRNA. Targeted deletion of Dicer from the proximal tubular epithelium protects from I/R-induced renal injury (preserved renal function, blunted tissue damage and tubular apoptosis, and survival benefit) and is associated with changes in the expression of distinct microRNAs (e.g., miR-132, -362, and -379) [36]. Furthermore, microvesicles secreted by endothelial progenitor cells and enriched with microRNA (including miR-126 and miR-296) were shown to ameliorate IRI in the murine kidney [37].

Taken together, ROS dominated in I/R-induced kidney injury.

Effects of ROS on the Stenotic Kidney

Vascular Function (Renal Perfusion and Endothelial Function)

A significant renal artery stenosis leads to persistent reduction of renal parenchymal perfusion and eventually may lead to loss of kidney function. In mild renal artery stenosis, renal perfusion may be sustained if the post-stenotic pressure remains within the range of autoregulation [38]. However, with increasing severity of stenosis, renal adaptation reaches its limit and a fall in renal blood flow ensues. In chronic ARVD, the reduction of renal blood flow triggers multiple mechanisms of tissue and vascular injury that lead to progressive renal fibrosis. Activation of RAAS induces

Ang II-dependent release of ROS, which trigger cascades of inflammatory processes and perivascular/interstitial fibrosis, eventually cause irreversible kidney damage [39]. Sympathetic overactivity may further activate RAAS, enhancing oxidative stress [40]. Endothelial function is disturbed through an imbalance between vasoconstrictors (mainly endothelin) and vasodilators (such as NO and prostacyclin), and plays pivotal role in the pathogenesis of ARVD (Fig. 2.1). Moreover, ROS directly cause renal vasoconstriction, which in turn decreases renal blood flow and function.

Superoxide anion rapidly scavenges nitric oxide NO and could therefore blunt NO activity in the renal vasculature, induces endothelial dysfunction, which is the initial step in the pathogenesis of atherosclerosis and contributes to development of hypertension. Renovascular hypertension may be secondary to excess Ang II and increased oxidative stress [5], but in turn the mechanical stretch in hypertension may provoke an increase in oxidative stress [41]. After renal angioplasty, forearm blood flow response to acetylcholine was enhanced in renovascular hypertensive patients, suggesting improvement in endothelial function. The increase in maximal acetylcholine-induced vasodilation was associated with decrease in urinary excretion of 8- hydroxy-2′-deoxyguanosine (OHdG) and in serum concentration of malondialdehyde-low density lipoprotein (MDA-LDL) [42]. Co-infusion of the antioxidant vitamin C augmented acetylcholine-induced vasodilation before angioplasty but not after angioplasty [42]. Figure 2.3 show comparable findings in the stenotic kidney of pig ARVD, in which increased superoxide anion production (Dihydroethidium (DHE) staining) was associated with decreased renal blood flow and its response to acetylcholine, which was improved by anti-oxidant treatment. These findings suggest that endothelial function is impaired in both experimental models and a clinical setting, and that this impairment is at least in part caused by increased oxidative stress.

Tubular Integrity

The key feature of ischemic nephropathy is renal atrophy, which is precipitated mainly by tubular atrophy. In a rat renal artery partial clip model [43], progressive reduction in renal mass was observed during the evolution of renal injury. In the acute phase (2–8 days), both apoptosis and necrosis-induced cell death, but increased tubular epithelial cell labeling and mitoses indicated epithelial repair. In the chronic phase (10–28 days), when the mass of the ischemic kidney underwent significant reduction, only apoptosis contributed to cell death, and the level of tubular epithelial cell labeling and mitosis returned to near normal. Intratubular macrophages were observed to remove the apoptotic bodies. The area of the tubular epithelium was reduced in atrophic tubules, possibly due to apoptotic cell deletion, as well as cell shrinkage. A form of kidney hibernation with readily reversible tubular atrophy has been described in rat with renal artery stenosis induced by a 0.2-mm clip around the left renal artery [44]. Following 7 weeks of clipping and 2 concomitant weeks of

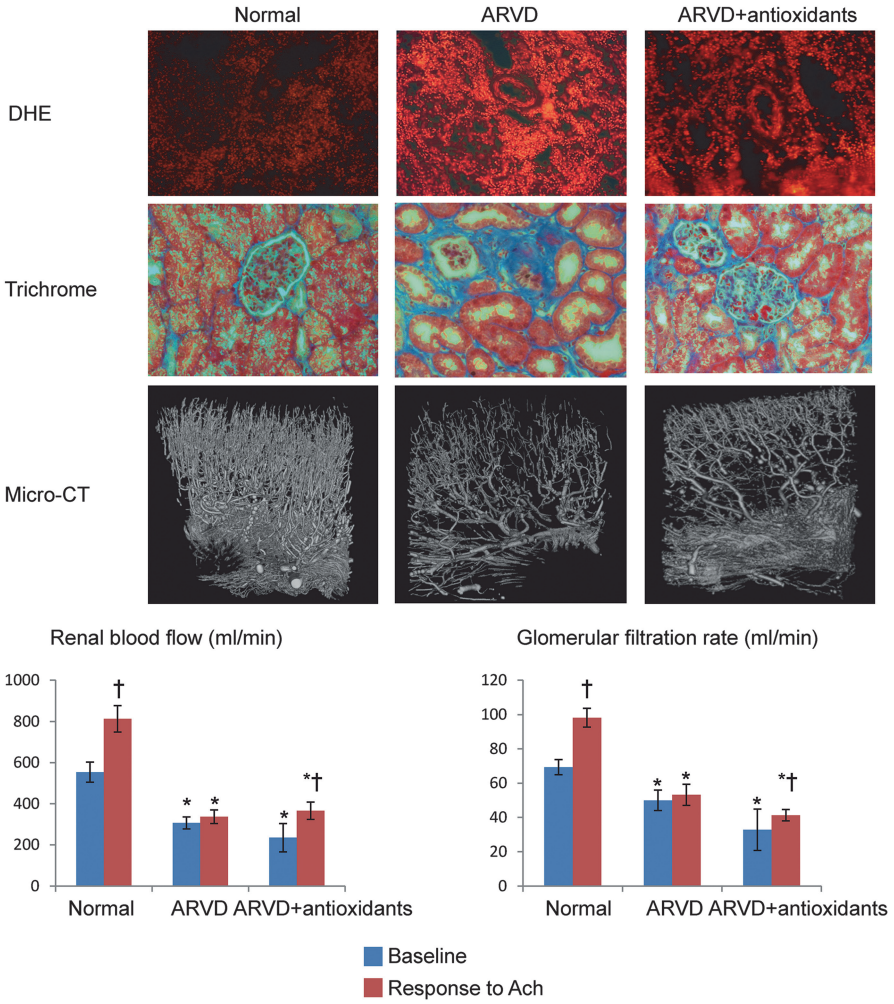

Fig. 2.3 Reactive oxygen species (ROS) and renal function, renovascular rarefaction, and renal fibrosis in porcine model of ARVD (with and without antioxidants). Representative images showing superoxide generation detected by dihydroethidium (DHE) staining and renal fibrosis by trichrome staining were increased in ARVD, and microcomputer tomograph (CT) images showing decreased microvascular density in ARVD, all were improved by antioxidants treatment. Furthermore, renal blood flow and glomerular filtration rate were both decreased in ARVD. Although antioxidants treatment didn't normalize renal function, renal blood flow response acetylcholine (Ach) was improved, suggest a role of ROS in endothelial dysfunction in ARVD

enalapril treatment, kidney length, renal blood flow, and glomerular filtration rate all decreased. Tubular cells were atrophic but not necrotic, accompanied by greatly reduced alkaline phosphatase in the tubular brush border and of acid phosphatase and peroxidase in lysosomes, while ATPase activity in the distal tubule segments remained unchanged. All observed changes were reversible within 2–3 weeks

following removal of the clip. Importantly, ROS induced by growth factor withdrawal act upstream of caspases in the apoptotic pathway, and induce tubular cell apoptosis [45]. After I/R, apoptotic cells appeared principally in the tubular epithelial cells, but not in the interstitial cells, thereby indicating that ROS are particularly harmful in tubule cells [46]. Ang II-induced activation of mitochondrial Nox4 is an important endogenous source of ROS, and is related to cell survival [16]. Furthermore, aldosterone can also induces apoptosis via ROS-mediated, CHOP-dependent activation in renal tubular epithelial cells [47].

Using computed tomography imaging, we found that intratubular fluid concentration (ITC, an index of tubular fluid reabsorption) was decreased in both the proximal tubule and Henle's loop in ARVD compared to non-atherosclerotic renal artery stenosis. This might have represented early functional injury in these tubular segments [8].

Glomerular Function

GFR is determined by both renal blood flow and glomerular capillary hydrostatic pressure. When renal perfusion pressure falls distal to a stenotic site, the afferent arteriole dilates while the efferent arteriole constricts, resulting in increased filtration pressure. These intrarenal compensatory mechanisms maintain GFR and renal blood flow despite reductions in renal perfusion pressure by up to 40 % [48, 49]. However, the limited range of kidney autoregulation may restrict renal adaptation and may be impaired after prolonged hypoperfusion or hypertension. "Ischemic nephropathy" may ensue, which is defined as an obstruction of renal blood flow that leads to ischemia and excretory dysfunction. Global, focal, or segmental glomerulosclerosis have been found in both experimental [50] and clinical [2, 51] ARVD, but are usually late sequelae or associated with comorbidities. Furthermore, in patients with atherosclerotic nephropathy the severity of histopathological damage, including glomerulosclerosis and interstitial fibrosis, is an important determinant and predictor of renal functional outcome [2, 51].

Polymorphonuclear Neutrophls (PMN) play an important role in glomerular injury due their ability to release highly toxic ROS generated by the myeloperoxidase (MPO)-hydrogen peroxide-halide system. Rats infused with MPO showed marked glomerular injury to the endothelium and mesangial cells, as well as fusion of the glomerular epithelial foot processes and cationic MPO to glomerular basement membrane [52]. Recent studies showed that neutrophil-to-lymphocyte ratio was positively correlated with TNF-α in patients with end-stage renal disease. Importantly, ROS-induced renovascular constriction is inhibited by ROS scavengers [53], and antioxidants attenuate glomerulosclerosis in experimental ARVD [54]. Figure 2.3 shows GFR was significantly decreased in the stenotic kidney of pig ARVD, in association with increased DHE staining, indicating the important role of ROS in glomerular function.

Renal Fibrosis

In a patient cohort study, a significant correlation was observed between renal functional outcome and interstitial volume, suggesting interstitial fibrosis as an important determinant and predictor of renal functional outcome [51]. Histologic evaluation of biopsies from the stenotic kidneys of patients with subtotal atherosclerotic vascular occlusion demonstrate widespread tissue TGF-β staining associated with reduced blood flow. TGF-β expression was elevated despite relative preservation of tissue oxygenation in this ARVD cohort with relatively preserved renal function [55]. More severe decrements in blood flow were associated with higher severity of tissue fibrosis and tubular atrophy. In ARVD inflammatory cellular infiltrates, particularly CD68+ macrophages, were more prominent in both subtotal and total occlusion compared with biopsies from normal kidney donors, and their overall number correlated with TGF-β score [55]. Upregulation of TGF-β is also commonly observed in experimental renal artery stenosis [56, 57]. TGF-β expression is elevated in poststenotic kidneys during their remodeling process, and stimulates expression of MCP-1 in mesangial cells through pathways involving ROS generation, suggesting that this cascade promotes progressive renal disease. Indeed, abrogation of TGF-β/Smad3 signaling pathway confers protection against development of fibrosis and atrophy in murine renal artery stenosis [57]. Importantly, evidence indicates that ROS (H_2O_2) direct induce TGF-β1 synthesis and thereby increases extracellular matrix gene expression in cultured human mesangial cells [58]. These cellular responses may underlie the development and progression of renal fibrosis characterized by oxidative stress.

Expression of the pro-fibrotic mediators TIMP-1 and PAI-1 is upregulated in the stenotic kidney, and both localize to the tubular and interstitial compartments [59]. TIMP-1 inhibits extracellular matrix degradation, leading to accumulation of fibroblasts and collagen deposition, while PAI-1 plays an important role in Ang II-mediated hypertensive kidney and heart injury. Recent study showed that increased aortic collagen and elastin content in the early phase of renovascular hypertension, possibly as a result of increased vascular NAD(P)H oxidase activity and oxidative stress [60]. Therefore, treatment approaches targeted to block oxidative stress might prevent development of fibrosis and subsequent renal dysfunction.

Microvascular Architecture

Microvascular rarefaction in the stenotic kidney accelerates progression of renal injury in ARVD (Fig. 2.1). Microvessels (vessels <500 μm in diameter) are responsible for delivery of blood to the renal parenchyma and possess unique abilities to adapt to local metabolic demands, sustaining renal function in early stages of ARVD. Therefore, alterations in microvascular structure or function may lead to hypoperfused and hypo-oxygenated regions in the kidney, triggering matrix

accumulation, interstitial fibrosis, and renal dysfunction. Importantly, reduced renal blood flow affects not only the number of microvessels in the stenotic kidney but also their structure and functionality. Indeed, Fig. 2.3 shows 3D microcomputed tomography images obtained from stenotic-kidney of ARVD pigs 10 weeks after induction of renal artery stenosis, illustrating significant impairment of the microvascular architecture and spatial density. Furthermore, decreased microvascular density was associated with enhanced oxidative stress. Importantly, antioxidants treatment partially restored microvascular density, underscore the role of ROS in microvascular remolding in ARVD [59].

Multiple pathways may contribute to microvascular damage in the stenotic kidney, including oxidative stress, apoptosis, inflammation, and fibrosis. In healthy men exposed to 12 h of sustained poikilocapnic hypoxia, 8-OHdG, advanced oxidation protein products, and vascular endothelial growth factor (VEGF) were increased in plasma and hypoxia inducible factor (HIF)-1 alpha mRNA was increased in leukocytes, suggest that hypoxia induces oxidative stress via an overgeneration of reactive oxygen species (ROS) [61]. Furthermore, Ang II can also increase HIF-1alpha in vascular smooth muscle cells to levels that are substantially more elevated than the hypoxic treatment [62]. However, hypoxia-induced ROS-dependent VEGF upregulation tend to increase vascular permeability, which were evidenced in human pulmonary artery endothelial cell (HPAEC) monolayers exposed to hypoxia, and treatment with antioxidants lowered the hypoxia-induced HPAEC monolayer permeability as well as the elevation of HIF-1alpha and VEGF [63]. Furthermore, downregulation of angiogenic factors like VEGF is often observed in the stenotic kidney [64] and is associated with decreased spatial density of cortical and medullary microvessels and enhanced oxidative stress, suggesting that ROS may impair HIF-VEGF pathway and contribute to vascular rarefaction. Indeed, ROS-dependent extracellular matrix depositing may limit microvessel sprouting, which also contribute to microvascular rarefaction in the stenotic kidney in ARVD.

Thus, ROS are involved in all major components of kidney injury in the stenotic kidney in ARVD, including endothelial dysfunction, glomerulosclerosis, microvascular rarefaction, and renal fibrosis.

Effects of ROS on the Non-stenotic Kidney

Vascular Function

The kidney damage in the non-stenotic kidney is mainly caused by hypertension. Typically, non-stenotic kidneys tend to have milder damage than post-stenotic kidneys [65]. In mice 2K1C model 11 weeks after renal artery stenosis, contralateral kidney showed minimal histopathological alterations [66]. Johnson et al. [67] suggested two stages of hypertension-induced kidney injury. In the first stage renal vasoconstriction dominates in the absence of altered renovascular structure, while in the second stage, renal vasoconstriction persists when the external stimuli are

removed. In the first stage, as long as glomerular afferent arteriolar structures remain intact, renal autoregulation effectively prevents transmission of increases in systemic blood pressure to renal glomeruli or peritubular capillaries. This is accomplished by two intrarenal mechanisms: (1) the afferent arteriolar myogenic response, which is a reflex causing afferent arterioles to constrict in response to increased arterial pressure [68]. (2) Tubuloglomerular feedback, which alters afferent tone in response to altered Na and Cl concentrations in distal tubule as it passes the macula densa [69]. In stage two, patients develop salt sensitivity, renal arteriolar dysfunction, and impaired renal autoregulation. This stage constitutes a risk for developing microalbuminuria and progressive renal disease, which eventually results in end stage renal disease. Increased ROS induced by Ang II and elevated pressure also induces renal tissue hypoxia, since increased O_2 utilization is not compensated by increased O_2 delivery [70]. Sustained hypoxia induces fibrogenesis and tubular atrophy, which together with renovascular dysfunction, result in progressively diminishing kidney function. Ang II influences vascular tone via two distinctly different receptors; activation of AT1R causes vasoconstriction, whereas activation of AT2-receptors induces NO release and causes vasodilation [71]. Normally, AT1 receptors are more abundant, and constriction, therefore, dominates the vascular response to Ang II. Even a short-term exposure of vascular smooth muscle cells to Ang II results in contractile dysfunction [72]. These alterations result in hypertension and vascular and tubulointerstitial damage. Furthermore, renal damage and proteinuria are improved by inhibiting Ang II signaling in spontaneously hypertensive rats (SHR) but unaffected by similar blood pressure-lowering treatment with the calcium channel blocker amlodipine [73]. ROS may play important role in above pathophysiological alterations in the contralateral kidney. In experimental study, 30 min of unilateral renal ischemia (UI) resulted in gradual increase in contralateral kidney weight over time and increased superoxide formation. After UI, there was a significant increase in the number of NADPH oxidase 2 (Nox2)-expressing cells and the level of Nox2 expression in the contralateral kidney was observed. Treatments with superoxide dismutase (SOD) mimetic and apocynin (a putative NADPH oxidase inhibitor) inhibited UI-induced hypertrophy of CLK along with reduction in Nox2-positive cell, and superoxide formation [74]. Thus, renal mass reduction by UI may increase ROS formation in the contralateral kidney then subsequently structural and functional impairment.

Tubular Function

In a 2k1c model, unclipped kidney hypertrophy is considered to be a compensatory mechanism driven by growth factors. Hypertrophy of the renal tubular cells, especially those of the proximal tubule, accounts for the majority of the increase in kidney size that follows loss of renal mass in the stenotic kidney [75]. Epidermal growth factor (EGF) may drive the growth of proximal tubular cells in the contralateral rat kidney, as its expression increases 5 and 14 days post nephrectomy [76].

Furthermore, stretch caused an increase in EGF receptor phosphorylation and cytosolic to membrane translocation of the p47phox NAD(P)H oxidase subunit. Hydrogen peroxide also elicited contraction through EGF receptor phosphorylation [41]. In unilateral nephrectomized rats, secretion of IL-10 and TGF-beta by mesangial cells of the remaining kidneys contributes to the hypertrophy of tubular cells [77]. In a double transgenic mouse, activation of TGF-β signaling in the tubular epithelium alone was sufficient to cause AKI characterized by marked tubular cell apoptosis and necrosis, oxidative stress, dedifferentiation and regenerative cell proliferation, reduced renal function, and interstitial accumulation of inflammatory cells. This tubular injury was associated with mitochondrial-derived generation of ROS [78]. TGF-β1 treated renal tubular epithelial NRK-52E cells showed upregulated NAD(P)H oxidase subunit p67phox mRNA and significantly increase NAD(P)H oxidase-dependent intracellular ROS, MCP-1, and IL-6 expression [79]. Thus, TGF-β may be a mechanistic link between acute injury and chronic progression of kidney disease. Moreover, ROS-induced tubular cell apoptosis also contribute to tubular injury. Treatment with various doses of the aldehyde products of lipid peroxidation 4-hydroxy-2-hexenal (HHE) resulted in dose-dependent decreases of cell viability and increases of ROS. HHE decreased the expression of Bcl-2, while it increased that of Bax, which induced apoptosis [80].

Glomerular Function

Less attention has been paid to nephropathies and proteinuria in the contralateral kidney in ARVD. A clinical study in a small number of patients showed decreased GFR in the stenotic kidney and increased in the contralateral kidney compared with the right kidney of essential hypertension [81]. Focal segmental glomerulosclerosis and nephrosclerosis were found in contralateral kidney biopsies from patients with ARVD [82, 83]. Possibly, besides the increase in renal perfusion pressure, activation of RAAS might promote glomerular hyperfiltration through vasoconstriction of the efferent arterioles in the contralateral kidney. Focal segmental glomerulosclerosis-like lesion thus induced appeared to have caused massive proteinuria [84].

Importantly, increased perfusion pressure in the contralateral kidney induces oscillatory shear, which is associated with stretch of endothelial and vascular smooth muscle cells, which can directly activate NAD(P)H oxidase to generate ROS [85]. This effect may be amplified by activation of the RAAS. Increased oxidative stress in response to stretch contributes to activation of pro-inflammatory transcription factors, activation of growth-promoting mitogen-activated protein (MAP) kinases, upregulation of pro-fibrogenic mediators, and altered vascular tone, important processes contributing to the glomerulosclerosis in the contralateral kidney.

Renal Fibrosis

The contralateral kidney in a pig model of renal artery stenosis shows a modest increase in interstitial fibrosis compared with normal, and macrophage infiltration in these kidneys implicates inflammatory mechanisms [86]. ROS may mediate interstitial fibrosis in ARVD. A study uses type 2 diabetic (db/db) mice and in db/db transgenic (Tg) mice overexpressing rat catalase showed that Tg mice had significantly attenuated renal fibrosis and tubular apoptosis, indicating the pivotal role of ROS in the development of hypertension-induced renal fibrosis [87]. Furthermore, matrix metalloproteinases (MMPs) are important regulators for extracellular matrix remodeling and their expression were upregulated by increased formation of ROS [88]. Antioxidant approaches attenuated the increases in MMP-2 expression/activity and the vascular remodeling associated with 2K-1C hypertension [89].

We have mentioned that shear stress may induce ROS formation in renovascular hypertension, it may also be involved in the development of renal fibrosis. A recent study [90] reported that human renal tubular cells (HK-2) exposed to fluid shear stress promote human THP-1 monocytes toward the inflammatory M1-type macrophage. Fluid shear stress-injured HK-2 cells expressed and secreted early biomarkers of tubular damage such as kidney injury-molecule-1 and neutrophil gelatinase-associated lipocalin. Thus, changes in fluid shear stress should now also be considered as potential insults for tubular cells that initiate/perpetuate interstitial inflammation. In vitro experiments using proximal tubule epithelial cells demonstrated that pathological shear stresses induces TGF-beta1-SMAD pathway, which is mediated by Notch4 [91].

Microvascular Architecture

Unlike the striking microvascular remodeling in the stenotic kidney, vascular adaption in the contralateral kidney in unilateral renal artery stenosis may resemble that observed in other forms of hypertension, and includes intrarenal arterial hypertrophy. In SHR, the walls of the interlobar, arcuate, and interlobular arteries appear to be hypertrophied in both the “pre-hypertensive” phase and in established hypertension, which is not reversible by chronic angiotensin converting enzyme inhibition. It is not easy to document changes in wall dimensions of intrarenal arteries during the development of human hypertension, but renal hemodynamic abnormalities currently attributed to renal vasoconstriction in early human hypertension are also compatible with renal arterial hypertrophy. These abnormalities include increased resting renal vascular resistance and augmented renal vascular resistance responses to vasoconstrictor agents. Hypertrophy of the renal vasculature to increase pre-glomerular resistance may have dual effects: increased renal vascular resistance, and effects on renal hemodynamics distally in a manner similar to narrowing of the main renal artery [92]. Intrarenal arterial hypertrophy may be induced by Ang II mediated pleiotropic vascular effects through NAD(P)H oxidase-derived ROS. Furthermore

oscillatory shear stress induced by hypertension is linked to increased ROS production with consequent oxidative damage. Induction of these signaling cascades leads to vascular smooth muscle cell growth and migration, expression of pro-inflammatory mediators, and modification of extracellular matrix [85].

Although studies on the pathophysiology of the non-stenotic kidney are much less intense, ROS clearly played important role in vascular and tubular injury. Preserve renal function in the non-stenotic kidney may be more important compared with restore damaged stenotic kidney.

Effects of ROS on Blood Pressure

Evidences of oxidative stress have been found in most experimental models of hypertension. Mice with ROS-generating enzyme deficiencies have lower blood pressure compared with wild-type counterparts [93], and fail to induce hypertension after Ang II infusion [94]. Thus ROS are critical in Ang II-induced hypertension, at least in animal models. However, most human studies showing only indirect associations between ROS and blood pressure. ROS participate in several redox-sensitive pathways involving the development of hypertension, particularly in the vasculature, kidney, and central nerves system. Superoxide anion and H_2O_2, act as second messengers in a highly regulated manner, stimulate MAP kinases, tyrosine kinases, Rho kinase, and transcription factors (NF-κB, activator protein -1, and HIF-1), inactivate protein tyrosine phosphatases, and proinflammatory gene expression and activity [95, 96]. In the vasculature, these alterations lead to endothelial dysfunction, reduced vasodilation, enhanced contraction, and structural remodeling, which in concert increase peripheral resistance and elevate blood pressure. In the kidney, activation of redox-sensitive pathways is associated with glomerular damage, proteinuria, sodium and water retention, and nephron loss, all of which are important in the development of hypertension. In the central nerves system, ROS produced by NAD(P)H oxidase in the hypothalamic and circumventricular organs are implicated in central control of hypertension [97, 98], in part through sympathetic outflow. Although oxidative stress may play a role in the pathophysiology of hypertension and associated target-organ damage, it is likely not the sole cause of blood pressure elevation. Ang II is a potent inducer of oxidative stress and Ang II-dependent hypertension is particularly sensitive to Nox-derived ROS [99]. Despite abundant experimental data supporting an etiological role for oxidative stress in the pathogenesis of hypertension, there is no confirmation that oxidative stress is a primary cause of hypertension in humans. Nevertheless, there is evidence that ROS bioavailability is increased in patients with essential hypertension, renovascular hypertension, malignant hypertension, salt-sensitive hypertension, cyclosporine-induced hypertension, and pre-eclampsia. Moreover, a link between oxidative stress and cardiovascular injury and hypertension associated target organ damage has been suggested [100]. Most clinical study findings are based on increased levels of plasma thiobarbituric acid-reactive substances and 8-epi-isoprostanes, biomarkers of lipid peroxidation, and oxidative stress.

Interventions to Decrease ROS in ARVD

Antioxidants

In experimental settings, natural or synthesized antioxidants have been applied for protection of kidney in renovascular disease [89, 101]. SOD mimic tempol normalized blood pressure in SHR in both short term and long term administration [102, 103], suggests a role for oxygen radicals in the maintenance of hypertension in SHR. Long-term feeding of blueberry-enriched diet lowered blood pressure, preserved renal hemodynamics, and improved redox status in kidneys of hypertensive rats and concomitantly demonstrated the potential to delay or attenuate development of hypertension-induced renal injury [104]. We supplemented antioxidant vitamins in a swine model of ARVD [54]. Kidney hemodynamics and function were quantified after 12 weeks of experimental ARVD (simulated by concurrent hypercholesterolemia and renal artery stenosis) with or without daily supplemented with antioxidant vitamins C (1 g) and E (100 IU/kg). We found that basal RBF and GFR were decreased in the stenotic kidney of ARVD pigs regardless of antioxidant supplement, but RBF and GFR response to acetylcholine that was blunted in ARVD significantly improved in vitamin-treated pigs. Vitamins also showed increased renal expression of endothelial nitric oxide synthase and decreased expression of NAD(P)H-oxidase, nitrotyrosine, inducible-nitric oxide synthase, and NF-κB, suggesting decreased superoxide abundance and inflammation. Furthermore, decreased expression of pro-fibrotic factors in vitamin-treated pigs was accompanied by augmented expression of extracellular (matrix metalloproteinase–2) and intracellular (ubiquitin) protein degradation systems, resulting in significantly attenuated glomerulosclerosis and renal fibrosis. Thus, chronic antioxidant intervention in early experimental ARVD improved renal endothelial function, enhanced tissue remodeling, and decreased structural injury. In human studies, the variable results of antioxidant vitamin intervention observed in clinical studies [105–107] are likely related to differences in study population, the duration, dose, and type of supplements, as well as outcome measures. The feasibility of applying antioxidant strategies for preserving the atherosclerotic and ischemic kidney still needs further investigations.

Although there may be some debate about whether it is NAD(P)H oxidase or other oxygenases responsible for kidney damage in hypertension, it is clear that reduction in NAD(P)H oxidase activity, and hence ROS, can ameliorate glomerular filtration barrier injury. Novel approaches to block NAD (P)H oxidase activity including gp91 ds-tat, siRNA [108], and monoclonal antibodies are being tried and hold great promise for not only hypertension but also for other disease processes with elevated oxidative stress.

Mitochondria are the important source of ROS. Recently, we have applied Bendavia, a novel tetrapeptide that inhibits mitochondrial permeability transition pore opening, in swine ARVD, and demonstrated that it protects the stenotic kidney by reducing oxidative stress and apoptosis [109, 110].

RAAS Inhibitors

Medical therapy is the cornerstone of treatment for ARVD, either alone or in combination with revascularization. The goals are reducing anatomic progression of the lesion and the impact of its consequences, improving blood pressure control, preserving renal function, slowing the rate of progression to ESRD, and reducing cardiovascular events. Inhibition of the RAAS with ACE inhibitors and angiotensin receptor blockers (ARBs) affords cardiovascular morbidity and mortality benefits in patients with cardiovascular risk [111]. Furthermore, RAAS inhibition reduces proteinuria and may delay ESRD in patients with renal dysfunction [112]. ACEI and ARB are effective in hypertension treatment in the presence of ARVD. There is some evidence that ACE inhibitors have the most potent blood pressure-lowering effect in these patients [113]. Furthermore, in nonrandomized studies of patients with ARVD, ACE inhibitor use was independently associated with survival benefit regardless of whether patients underwent revascularization [114, 115]. Similarly, in a cohort study [116] of 3570 patients with ARVD, ACE inhibitor use was associated with a lower risk for the primary composite outcome of death, and dialysis initiation [117]. Despite the potential benefits, use of RAAS inhibitors need to be monitored closely in patients with ARVD, as precipitous declines in GFR may occur. Caution should be taken in patients with older age, higher baseline creatinine (>2.0) and/or lower eGFR (<35), although a prospective cohort study reported that eGFR improved following discontinuation of RAAS blockade [118].

The mechanisms for improvement in renal function and/or proteinuria by RAAS inhibitors are not only related to their blood pressure lowering effects, but also depend on their anti-oxidant, anti-inflammatory, and anti-fibrotic effects. In transgenic rat models and genetic models of hypertension and glomerular filtration barrier injury, the ARBs/ACE inhibitors valsartan, irbesartan, and losartan reduced blood pressure, and the tissue benefits were beyond that anticipated by BP control alone including amelioration of proteinuria, slit diaphragm widening, podocyte effacement, decrease in number of slit pores and basement membrane widening. Furthermore, these treatments decreased perivascular fibrosis and oxidative stress (3-nitrotyrosine in glomeruli, 8-OHdG in urine, NAD(P)H oxidase activity, enzyme subunits by western blots and immunohistochemistry). No specific clinical trial has been designed to test the anti-oxidant property of AECI/ARB. However, in 53 nondialyzed hypertensive CKD patients taking ACE inhibitor or calcium blocker, serum and urinary 8-OHdG were determined. In comparison to a calcium channel blocker, an ACE inhibitor seems much more protective against oxidative DNA damage in hypertensive patients with different stages of CKD [119].

Percutaneous Transluminal Renal Angioplasty (PTRA)

The rationale for renal artery revascularization is to relieve obstruction to flow and downstream ischemia, as well as to reduce activation of the RAAS and the subsequent cascade of pathophysiological processes. Although early nonrandomized

studies showed some benefits of revascularization in ARVD [120, 121], recent large clinical trials revealed that renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in patients with ARVD and hypertension or chronic kidney disease [122]. In experimental ARVD, we found that 4 weeks after renal artery stenting blood pressure was normalized. However, GFR and RBF remained unchanged. Microvascular rarefaction was unaltered after revascularization, and the spatial density of outer cortical microvessels correlated with residual GFR. Interstitial fibrosis and altered expression of proangiogenic and profibrotic factors persisted after stenting. Microvascular loss and fibrosis in swine ARVD might account for persistent renal dysfunction after revascularization and underscore the need to assess renal parenchymal disease before revascularization [123]. Interestingly, Ziakka et al. found that oxidative stress was the strongest predictive factor for serum creatinine increase in these patients who failed to improve renal function after revascularization [121]. We also implicated inflammation in the inability of PTRA to fully reverse renal damage in the post-stenotic kidney [124, 125]. On the other hand, renal angioplasty decreased plasma renin activity, plasma AngII concentration, and serum MDA-LDL concentration and urinary 8-OHdG excretion in patients with renovascular hypertension, and forearm blood flow response to acetylcholine was enhanced, suggest that PTCA may attenuate oxidative stress in a clinical setting [42].

Stem Cells

Mesenchymal stem cells (MSC) confer renal protection through paracrine/endocrine effects, and their anti-inflammatory and immune-modulatory properties target multiple cascades in the mechanisms of ischemic kidney in ARVD. As discussed previously, clinical trials have not identified major benefits for PTRA [126], likely due to lingering kidney tissue damage. To improve its efficiency, we replenished MSC as an adjunct to experimental PTRA in ARVD pigs [127]. PTRA was performed 6 weeks after renal artery stenosis, with adjunct delivery of adipose tissue-derived-MSC (10×10^6 cells). Four weeks after successful PTRA, mean arterial pressure fell to similar levels in all revascularized pigs. MSC restored stenotic-kidney GFR and RBF, which remained low after PTRA alone. Interstitial fibrosis, inflammation, microvascular rarefaction, and oxidative stress were also attenuated to a greater degree in PTRA + MSC-treated pigs. This study suggested a novel therapeutic potential for MSC in restoring renal function and blunting structural remodeling when combined with PTRA in ARVD.

The mechanisms by which MSC achieve renal cellular repair are multifactorial. MSC ameliorate I/R-induced renal dysfunction by improving the antioxidant enzymes superoxide dismutase and glutathione peroxidase levels [128] and through enhancing NAD(P)H quinone oxidoreductase-1 and HO-1 activities, two indicators of anti-oxidative capacity [129]. Furthermore, MSC may release growth factors or

anti-inflammatory cytokines to the injury site. MSC release microparticles carrying anti-inflammatory cytokines and growth factors that promote kidney repair by their internalization in tubular or other cells. All these actions tone down intra-renal inflammation and oxidative stress, and allow for vascular regeneration. Moreover, anti-apoptotic effects of MSC [130] can prevent cell loss.

Summary

In summary, ROS played pivotal role in the pathophysiology of ARVD, in both acute and chronic renal injuries. Interventions with antioxidants have different effects on blood pressure. SOD mimic tempol was able to normalize blood pressure in SHR, reflects that ROS is the major factor in the maintenance of hypertension in this model. While antioxidant vitamins have potential to improve renal function in experimental ARVD but failed to normalize blood pressure, suggest that ROS is not the only mechanism in renovascular hypertension. Although we have gained plenty of knowledge in ROS formation and their signaling in different diseases, the basic physiological role of ROS is still not clear. We may still a few steps away from fully understand the entire picture of ROS. Nevertheless, blockade of RAAS using ACEI/ARB have showed potential of attenuation of oxidative stress while improving clinical outcome in ARVD. Stem cells combine with PTRA has promising results in experimental ARVD and translational studies are urgently needed in this area.

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