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Mechanisms of Tissue Injury in Renal Artery Stenosis: Ischemia and Beyond

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Abstract

Renal injury distal to an atherosclerotic renovascular obstruction reflects multiple intrinsic factors producing parenchymal tissue injury. Atherosclerotic disease pathways superimposed on renal arterial obstruction may aggravate damage to the kidney and other target organs, and some of the factors activated by renal artery stenosis may in turn accelerate the progression of atherosclerosis. This cross talk is mediated through amplified activation of renin-angiotensin system, oxidative stress, inflammation, and fibrosis, pathways notoriously involved in renal disease progression. Oxidation of lipids also accelerates the development of fibrosis in the stenotic kidney by amplifying profibrotic mechanisms and disrupting tissue remodeling. The extent to which actual ischemia modulates injury in the stenotic kidney has been controversial, partly because the decrease in renal oxygen consumption usually parallels a decrease in renal blood flow, and because renal vein oxygen pressure in the affected kidney is not decreased. However, recent data using novel methodologies demonstrate that intra-renal oxygenation is heterogeneously affected in different regions of the kidney. Activation of such local injury within the kidney may lead to renal dysfunction and structural injury, and ultimately unfavorable and irreversible renal outcomes. Identification of specific pathways producing progressive renal injury may enable development of targeted interventions to block these pathways and preserve the stenotic kidney.

Keywords

renal artery stenosis; atherosclerosis; ischemia

BACKGROUND

Renovascular nephropathy is becoming more frequently identified in patients with chronic and end-stage renal disease as the population ages. Significant renal artery stenosis (RAS) ($\geq 60\%$ lumen occlusion), usually caused by atheromatous plaques, is present in almost 7% of adults older than 65 (1) and up to 50% of patients presenting with diffuse atherosclerotic disease (2). In addition to threatening renal function, atherosclerotic renovascular disease with renal

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failure poses a risk for exacerbation of cardiovascular disease (3,4) and predicts cardiovascular mortality (5,6). Hence, the mechanisms responsible for renal and cardiovascular damage in this disease are being vigorously sought, and effective therapeutic strategies to preserve the kidney are under intense investigation.

Several recent lines of evidence highlight the pathophysiological complexity of atherosclerotic renovascular disease. The elusive nature of this disease is underscored by the poorer outcomes compared to fibromuscular dysplasia (7), which comprises the second most common etiology for RAS and involves a localized renal arterial lesion. Restoration of vascular patency for fibromuscular dysplasia regularly produces “cure” and improvement for renovascular hypertension (8). By contrast, results from recent clinical trials for patients with atherosclerotic renovascular disease indicate that revascularization with percutaneous transluminal renal angioplasty (PTRA) and stenting improve blood pressure (9) or recover renal function (10, 11) inconsistently. Surgical correction of atherosclerotic renovascular disease also results in blood pressure benefit and retrieval of renal function only in selected patients (12), arguing against technical failures of PTRA as a major cause of the muted response of renal function to revascularization in atherosclerotic RAS. As a result of the uncertainty regarding outcomes, several clinical trials, such as Angioplasty and STent for Renal Artery Lesions (ASTRAL) (13) and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) (14) trials, are in the process of examining the benefits of revascularization compared to medical treatment alone to improve renal function in these patients.

Additional evidence advances the notion that RAS itself is not the only mechanism affecting the kidney in atherosclerotic renovascular disease. In contrast to patients with fibromuscular dysplasia, the decrease in renal perfusion (15) and function (16) does not correlate with the angiographic degree of stenosis for patients with atherosclerotic RAS. Important support for this observation is derived from the correlation between renal functional outcome and chronic renal damage score, glomerulosclerosis, and interstitial volume in ‘atherosclerotic nephropathy’, or renal pathology in the presence of disseminated atherosclerosis (17). A corollary of this correlation is that the severity of histopathological damage is an important determinant and predictor of renal functional outcome even in the absence of hemodynamically significant RAS (17).

Because renal functional outcomes are only loosely linked to renal arterial patency in atherosclerotic RAS, additional mechanisms must determine renal injury. However, the major factors responsible for renal tissue injury in RAS are yet unidentified. While pre-existing and co-existing risk factors (e.g. aging, renal disease, essential hypertension) likely amplify damage in the stenotic kidney, the decrease in renal perfusion in patients with atherosclerotic RAS exceeds that incurred in age- and treatment-matched patients with fibromuscular dysplasia with a similar degree of stenosis (15). Therefore, additional pathogenic factors inherent to the disease might contribute to renal damage in atherosclerotic RAS.

Factors that aggravate renal disease in atherosclerotic RAS likely involve synergistic interactions among disease mechanisms activated by diffuse atherosclerosis and those triggered by the super-imposed renal arterial obstruction. Maladaptive activation of the renin-angiotensin system as a result of the decrease in renal perfusion pressure as well as by dyslipidemia, circulating atherogenic factors that impact the renal parenchyma distal to the stenosis, and/or hypoxia secondary to renal arterial obstruction and oxidative stress, might all interact to amplify renal functional and structural damage.

Vascular dysfunction in atherosclerotic renovascular disease

Atherosclerotic renovascular disease involves co-existence of hypoperfusion, atherosclerosis, and cardiovascular risk factors, which activate mechanisms that promote renal functional

impairment and tissue injury. Conversely, some of the humoral factors activated in RAS accelerate the progression of atherosclerosis (18). Several deleterious pro-inflammatory and pro-fibrotic pathways that have been implicated in progression of renal damage in hypoperfused kidneys may also be activated in the kidney during the evolution of atherosclerosis (19). In both conditions renal functional impairment is initiated by endothelial injury, reduced bioavailability of the vasodilator nitric oxide, and increased activity of vasoconstrictors, all of which are common to both RAS and atherosclerosis. Renal microvessels are susceptible to noxious insults including ischemia, low shear stress, or oxidized low-density lipoprotein (ox-LDL), which compromise the integrity of the endothelium and prompt endothelial cells for early swelling and dysfunction (20). Consequent dysfunction of endothelial cells impairs vascular reactivity, endothelial barrier function, angiogenic capability, proliferative capacity, and migratory properties, and blunts protection from inflammatory cell infiltration. Furthermore, endothelial dysfunction in both these milieus is accompanied by increased generation of reactive oxygen species (ROS) and oxidative stress. These changes result in predominance of renal vasoconstrictors, enhanced renal vascular tone, and premature senescence.

ROS activate several pathways that modulate renal microvascular function. Taken together, ROS increase renal vascular tone, sensitivity to vasoconstrictors, endothelial dysfunction, and tubuloglomerular feedback that characterize pathophysiological conditions associated with increased oxidative stress (21). The interaction of ROS with nitric oxide decreases bioavailability of the latter, and at the same time results in formation of the pro-oxidant peroxynitrite. These effects combine to impair intra-renal vascular, glomerular, and tubular function (Figure 1). The result of quenched vascular nitric oxide is to limit its buffering effect, thereby allowing intra-renal vasopressors like angiotensin II and endothelin-1 to predominate with vasoconstriction and a decrease in glomerular filtration rate. This mechanism has the potential to impair both renal hemodynamics and function.

Since RAS and atherosclerosis are both characterized by increased oxidative stress, their co-existence augments the production of ROS and impairs renal function. Indeed, oxidative stress is increased in stenotic kidneys (22–24), and further exacerbated in the presence of co-existing early atherosclerosis, in association with amplification of renal dysfunction and injury (25, 26). Furthermore, reduced endogenous nitric oxide may interfere with a spectrum of additional activities of the molecule, such as loss of both its anti-thrombotic protection and inhibition of fibrosis-related responses to injury. Similar mechanisms might be involved in increased activity of growth factors and inflammatory mediators observed in RAS, eventuating in renal tissue injury.

Renal structural injury in atherosclerotic renovascular disease

The severity of histopathological damage is an important determinant of renal outcomes in patients with atherosclerotic nephropathy, regardless of the presence of RAS (17). When experimental RAS occurs, renal hypoperfusion leads to a mixture of adaptive responses, tubular and endothelial cell damage and repair events (27). Progressive renal failure can result from glomerulosclerosis, tubulointerstitial fibrosis, and/or vascular sclerosis. Glomerulosclerosis is a relatively late event in human RAS and often linked to long duration, pre-existing injury, and exacerbating co-morbid conditions, like dyslipidemia and atherosclerosis (27). Glomerular lesions are initially minimal in experimental models of chronic non-infarcted RAS (27) and observed only with severe stenosis nearing cortical infarction (28,29). The earliest and most pronounced pathologic features in renal ischemia consist of tubulointerstitial changes (27,30) that may mediate the progression of renal disease towards irreversible damage. At the early phase of this process cellular activation takes place, as mononuclear cells migrate into the interstitium and myofibroblasts/activated-fibroblasts release soluble products that contribute

to inflammation (31). This likely involves activation of inflammatory mediators like the redox-sensitive transcription factor nuclear factor kappa B (NFκB) (32), possibly through ROS release. Apoptosis may also be induced by ROS, and initially serves as a protective mechanism to induce tubular atrophy (33), but can also initiate inflammation and tissue injury (31). However, this phase may still be partly reversible until fibrosis begins (34) and eventuates in permanent parenchymal damage.

Cellular activation in the stenotic kidney elicits release of growth factors and cytokines, with primary roles suggested for angiotensin II, transforming growth factor (TGF)-β, and endothelin-1 (35), which also use ROS as second messengers. These in turn can stimulate production and activity of growth factors that modulate renal tissue response to ischemia-like collagen deposition, extracellular matrix turnover, fibrosis, and angiogenesis (Figure 1); excessive matrix accumulation finally leads to irreversible scarring. In addition, tubular injury alters the antigenic profile of the epithelial cells, and instigates a cascade of immune responses associated with infiltration of B-lymphocytes, T-lymphocytes, and macrophages. Similar processes accompany initiation of glomerular cell apoptosis, basement membrane thickening, and expansion of the mesangial extracellular matrix, which progress to glomerulosclerosis (36–38). NFκB is a pivotal player in this process, as its target genes include chemokines, adhesion molecules, and anti-apoptotic factors, such as matrix metalloproteinases -2 and -9. Furthermore, NFκB upregulates endothelin-1 expression, and might thus be also involved in vasoconstriction (39). Indeed, proteasome inhibitors, which decrease proliferation and inflammation partly by reducing activation of the NFκB, can improve renal endothelial function (40).

Little is known about molecular mechanisms of renal injury related to atherosclerosis itself in humans, but a series of studies in a pig model with diet-induced hypercholesterolemia, a surrogate for early atherosclerosis, reveal some of the mediators that might be activated at the early stages. Cellular and molecular events involved early in atherogenesis resemble those triggered in other forms of renal disease (19). Similar to RAS, dyslipidemia and atherosclerosis are pro-inflammatory conditions characterized by interstitial inflammatory infiltrates (41), NFκB activation (42), collagen deposition (43), growth factor production, altered matrix turnover (44), tubulointerstitial damage (45), and eventually glomerulosclerosis (46). In fact, it has been long recognized that glomerulosclerosis and atherosclerosis share similar pathophysiological mechanisms (47-50).

Hypercholesterolemia increases the availability of ox-LDL, which is cytotoxic to renal mesangial, epithelial, and endothelial cells, and can promote fibrosis by increasing intra- and extra-cellular matrix protein synthesis, as well as by decreasing its degradation (51). Hence, ox-LDL accelerates the development of fibrosis in the stenotic kidney by amplifying profibrotic mechanisms and disrupting tissue remodeling (Figure 1), alterations that contribute to microvascular remodeling and renal disease progression (26). Notably, angiotensin II stimulates both LDL oxidation and ox-LDL uptake, since it upregulates the expression of its receptor LOX-1 (52). LOX-1 is upregulated in hypercholesterolemia, upregulates the AT1 and its own receptor, and increases ROS production, instigating a cytotoxic cycle (53,54), since LOX-1 expression is also redox-sensitive. These effects might be exacerbated during co-existence of atherosclerosis and hypoperfusion, and thereby accelerate renal injury. Endothelin-1 (22) and oxidative stress (55) that are abundant in renovascular disease also regulate renal LOX-1 expression. Therefore, concurrent atherosclerosis may contribute to the evolution of renal damage, both directly through deposition of atherogenic and oxidized lipoproteins (56,57) and indirectly by increasing oxidative stress, since many of these processes, cytokines, and growth factors are redox-sensitive.

An additional important pathway by which atherosclerosis might contribute to renal disease progression includes impeding defense mechanisms that curtail structural damage and interfering with matrix turnover. Renal scarring and tissue remodeling are dynamic processes that involve both synthesis and degradation of extracellular matrix, the balance between which appears to be disrupted in several renal diseases. The accumulation of fibroblasts, excess collagen, and other matrix components leads to scar tissue formation. RAS kidneys with or without concurrent HC exhibit upregulated tubular and glomerular expression of pro-fibrotic factors like TGF- β , tissue inhibitor of metalloproteinase (TIMP)-1, and plasminogen activator inhibitor (PAI)-1. However, compared to RAS alone, coexistent HC increases the expression of NF κ B, attenuates the expression of extra-cellular (matrix-metalloproteinase-2) and intra-cellular (ubiquitin) protein degradation systems (44), and decreases apoptosis (that serves to eliminate damaged cells) in the kidney (26). Early atherosclerosis also induces tubular dysfunction (25) and elicits tubular epithelial-to-mesenchymal transition, a process shown to participate in several forms of renal disease (58). This suggests a shift in the tissue remodeling process in atherosclerotic RAS favoring tubular injury, matrix accumulation, and interstitial fibrosis (Figure 1).

In addition to tubulointerstitial injury, patients with atherosclerosis exhibit intra-renal microvascular disease leading to vascular rarefaction (27,34,59,60). This process represents an early phase of ischemic renal disease, which may initially produce functional abnormalities and evolves into permanent changes in microvascular structure. This is because prolonged periods of reversible vasoconstriction can cause lasting changes in the microcirculation, the most prominent of which are microvascular remodeling (e.g. an increase in wall/lumen ratio) and rarefaction (reduced number or combined length of peritubular capillaries within vascular beds) (61). Loss (rarefaction) of peritubular capillaries (62) and tubulointerstitial injury are prominent feature in renal ischemia and linked to renal dysfunction (Figure 1). A decrease in oxygen supply upregulates the expression of hypoxia-inducible factor (HIF)-1 α , and in turn of vascular endothelial growth factor (VEGF) that induces compensatory new vessel formation. However, prolonged or severe increases in oxidative stress may destabilize HIF-1 α protein and thereby interfere with tissue repair. Thus, chronic hypoxia itself may restrict compensatory angiogenesis and decrease its efficiency for restoring stenotic kidney perfusion. In addition, atherosclerosis can suppress new vessel formation by upregulating anti-angiogenic factors like thrombospondin, which in turn activates TGF- β , inhibits matrix metalloproteinases, and thereby disrupts matrix turnover (44). Indeed, decreased spatial density of microvessels characterizes stenotic kidneys (24,63) (Figure 2) and might be caused by decreased expression of HIF-1 α and VEGF proteins; both this protein expression and microvascular density can be improved by pro-angiogenic intervention (64). Since microvascular remodeling correlates with renal scarring (65), it may have important implication for renal disease progression in atherosclerotic renovascular disease.

What is the role of hypoxia in “ischemic renal disease”?

“Ischemia” refers to impaired blood flow below the level needed to satisfy the metabolic demands of the tissue, presumably leading to tissue hypoxia. While the term “ischemic nephropathy” suggests that impairment of renal function beyond occlusive disease of the main renal arteries results from hypoxia, the contribution of true hypoxia to renal damage in RAS has been controversial (66). Renal oxygen supply is among the highest in the body (Table 1) (67), so that less than 10% of delivered oxygen is needed to maintain renal metabolic needs. Interestingly, in patients with unilateral RAS a decrease in O₂ consumption appears to exceed the decrease in renal blood flow, based on the observation that oxygen-saturation in blood from the ischemic kidney is sometimes higher than that from the non-stenotic contralateral kidney (68). This may result from decreased glomerular filtration and tubular sodium reabsorption

that reduce oxygen consumption in the stenotic kidney (Figure 3). Hence, one might argue that loss of renal viability is not necessarily related to impaired oxygenation.

However, recent studies during acute RAS measuring intra-renal tissue oxygenation directly using oxygen electrodes have demonstrated in pigs that while graded decrements in renal blood flow were paralleled by decrements in oxygen delivery and consumption and sustained arterio-venous oxygen balance, regional renal tissue oxygenation declined (medullary more than cortical), supporting the existence of regional tissue hypoxia (69). Similarly, renal cortical PO_2 of chronically clipped kidneys is significantly lower than contralateral kidneys in early Goldblatt hypertensive rats (70). Thus, measures of whole kidney oxygen consumption may be insufficient to indicate the presence of localized ischemia and changes in tissue O_2 delivery and consumption. These observations are underscored by imaging studies in pigs employing Blood Oxygen Level-Dependent (BOLD) magnetic resonance imaging (MRI) that detects tissue deoxyhemoglobin signal, which have shown that BOLD signal of the cortex and the medulla increased during gradual renal arterial occlusion (indirectly implying a decrease in renal oxygenation) (71). Furthermore, BOLD MR studies in kidneys of patients with RAS confirm higher medullary deoxyhemoglobin levels compared to the cortex, although basal BOLD signal varies widely between individuals (72). In patients with high grade RAS but with preserved tissue volume and enhancement, the medullary and cortical BOLD signal are elevated and fall after intravenous furosemide (which inhibits energy-dependent renal transport and oxygen consumption) (72). These observations suggest that viable kidneys may show regional ischemic changes that are associated with tubular transport activity, and are thus attenuated by furosemide.

How, then, is renal vein oxygen saturation preserved or even increased from the stenotic kidney? Important differences in tissue oxygen requirements and delivery exist within regions of the kidney, leaving some areas vulnerable to reduced flow (72). These regional changes in oxygenation may be related to redistribution of sodium reabsorption along the medullary thick ascending limb of Henle's Loop, shifting of reabsorption from paracellular to transcellular pathways that increase stoichiometric energy requirements, and increased renal arterio-venous oxygen shunting (69).

Renal arterio-venous oxygen shunting has been proposed as a structural antioxidant defense mechanism that prevents PO_2 in the renal cortical microcirculation from increasing to hyperoxic levels commensurate with the high delivery of blood to the kidney. Studies in rabbits indicate that fractional extraction of oxygen falls with increasing renal blood flow without concomitant changes in intra-renal PO_2 , leading the authors to implicate arterio-venous oxygen shunting in regulation of intrarenal oxygenation (73). As much as 50% of inflowing oxygen from blood within preglomerular arterial vessels may undergo diffusional shunting to post-glomerular veins (Figure 4) speculatively preventing production of ROS in what could otherwise become a hyperoxic microenvironment (74). Renal oxygen consumption is also modulated by tubular work, the efficiency of tubular reabsorption (which in turn depends on ROS and nitric oxide), cellular hypertrophy, and possibly vascular wall oxygen consumption as well (75). Interestingly, experimental studies in a remnant kidney model indicate that tubular hypertrophy is associated with tubulointerstitial hypoxia as assessed by pimonidazole and upregulation of hypoxia-responsive genes (76). Conceivably, tubular atrophy in the stenotic kidney might conversely decrease O_2 consumption and offset hypoxia. On the other hand, microvascular dysfunction and rarefaction (24,63,64), inflammation, oxidative stress, and fibrosis in the stenotic kidney may all decrease the efficiency of tubular reabsorption (69), thereby limiting oxygen supply and diffusion (63). These processes ultimately may result in areas of heterogeneous, yet functionally consequential, intra-renal hypoxia that may not be reflected as a decrease in the whole kidney venous PO_2 .

Perspective

Taken together, cumulative evidence suggests that atherosclerosis has the potential to accelerate the detrimental effects of hypoperfusion on renal hemodynamics and function. Concurrent atherosclerosis may promote impairment in renal function and structure in atherosclerotic renovascular disease, and amplify activation of disease mechanisms (e.g. oxidative stress, inflammation, and fibrosis) in the stenotic kidney. Furthermore, it may accelerate irreversible renal injury and scarring, which impede recovery of the atherosclerotic RAS kidney following revascularization. Identification of pathways involved in renal injury progression may assist in development of targeted interventions that preserve the stenotic kidney.

For example, activation of the renin-angiotensin system is a hallmark of renovascular disease and characterizes atherosclerosis as well, but its blockade in RAS is potentially harmful, because of a consequent decrease in glomerular filtration rate. Nonetheless, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are often renoprotective in patients with chronic renal insufficiency, are generally not associated with total loss of filtration, and renal function usually does not further deteriorate during chronic treatment (77). Chronic blockade of oxidative stress pathways by supplementation of antioxidant vitamins E and C improves renal hemodynamics and decreases oxidative stress, inflammation, and fibrosis in the experimental ischemic kidney (22,23,78). These maneuvers also can restore microvascular architecture (24) (Figure 2). However, the disappointing results of clinical trials argue against indiscriminate use of antioxidants in human disease. More recently, intra-renal administration of progenitor cells has shown promise to improve the function and structure of the kidney subjected to chronic (64) or acute (79) ischemic injury. These observations underscore the urgent need to develop novel anti-inflammatory and anti-fibrotic strategies to attenuate renal injury.

In summary, elucidation of mechanisms involved in deleterious effects of concurrent atherosclerosis and renal artery stenosis on the kidney can advance our understanding of the pathogenesis of renal injury. Such studies may also be relevant to the effects of atherosclerosis upon other forms of nephropathy associated with ischemia (34).

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Figure 1.

Interplay of mechanisms by which atherosclerosis might aggravate kidney injury in renal artery stenosis. Angiotensin II and reactive oxygen species (ROS) regulate the expression of thrombospondin (TSP), transforming growth factor (TGF)- β , and tissue inhibitors of matrix metalloproteinases (TIMP), leading to a decrease in matrix metalloproteinases (MMP), accumulation of extra-cellular matrix, and fibrosis. Immune responses and inflammatory mediators such as nuclear factor kappa B (NF κ B), monocyte chemoattractant protein (MCP)-1, and tumor necrosis factor (TNF)- α , contribute to increase oxidative stress, formation of oxidized LDL (ox-LDL), and fibrosis. ROS also scavenge nitric oxide (NO) to form peroxynitrite (ONOO), thereby inducing endothelial dysfunction and loss of the vasculoprotective effects of NO. Similar mechanisms lead to loss of intra-renal microvessels. Modified with permission from (19).

Figure 2.

Tomographic images of the renal microcirculation showing microvascular rarefaction in the stenotic kidney (middle panel) compared to normal pig kidney (left), which was improved in RAS pigs treated with chronic antioxidant supplementation (right). The vessels on the cortex and medulla show interlobar vessels (I), arcuate vessels (arrow), and the branching orders of radial vessels (R) with numerous small vessels (*) in the outer third of the cortex (displayed at 40- μ m voxel size). Modified with permission from (24).

Figure 3.

The relationship between renal oxygen consumption and renal filtration rate (left) and sodium reabsorption rate (right). A decrease in renal metabolic activity is associated with a decrease in total renal oxygen uptake, constituting a mechanism to balance oxygen supply and demand. Modified with permission from (80).

Figure 4.

Arterio-venous oxygen shunting is likely to occur in the kidney, in which a counter-current arrangement allows close proximity of arteries and veins. This might be one of the mechanisms that regulate intra-renal oxygenation. The numbers represent oxygen tension along the nephron (mmHg).

Table 1

The estimated balance of oxygen consumption and delivery in different organs.

Region or organ	O ₂ Delivery (mL/min/100g)	Blood flow rate (mL/min/100g)	O ₂ Consumption (mL/min/100g)	O ₂ Consumption/O ₂ delivery (%)
Hepato-portal	11.6	58	2.2	18
Kidney	84.0	420	6.8	8
Outer medulla	7.6	190	6.0	79
Brain	10.8	54	3.7	34
Skin	2.6	13	0.38	15
Skeletal muscle	0.5	2.7	0.18	34
Heart	16.8	84	11.0	65

Modified with permission from (67).