



Published in final edited form as:

Adv Chronic Kidney Dis. 2015 May ; 22(3): 224–231. doi:10.1053/j.ackd.2014.10.004.

Atherosclerotic renal artery stenosis: Current status

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Abstract

Atherosclerotic renal artery stenosis (ARAS) remains a major cause of secondary hypertension and renal failure. Randomized, prospective trials show that medical treatment should constitute the main therapeutic approach in ARAS. Regardless of intensive treatment and adequate blood pressure control, however, renal and extra-renal complications are not uncommon. Yet, the precise mechanisms, accurate detection, and optimal treatment in ARAS remain elusive. Strategies oriented to early detection and targeting these pathogenic pathways might prevent development of clinical endpoints. Here, we review the results of recent clinical trials, current understanding of the pathogenic mechanisms, novel imaging techniques to assess renal damage in ARAS, and treatment options.

Keywords

Atherosclerosis; Renal artery obstruction; Ischemia; Inflammation; Hypertension

Introduction

Atherosclerotic renal artery stenosis (ARAS) (>60% lumen occlusion) is present in almost 7% of elderly people.¹ Attribution of ARAS as an etiology of end-stage renal disease is often difficult, especially in patients with vascular diseases, who often have increased burden of risk factors for parenchymal renal disease.² Nevertheless, experimental and observational cohort studies confirm that ARAS is an important contributor to renal failure and aggravating hypertension.^{3–5} In addition, ARAS with chronic kidney disease (CKD) poses a risk for exacerbation of cardiovascular disease and multiple long-term complications.⁶ Several cohort and clinical trials suggest therapeutic regimens such as angiotensin blockade and statins may slow the rate of loss of renal function over time.^{7,8} However, sub-groups of patients with ARAS experience rapid renal functional decline,⁹

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Conflict of interest: The authors declare no conflict of interest.

although its determinants are difficult to establish.¹⁰ Several lines of evidence highlight the pathophysiological complexity contributing to renal and cardiovascular damage in ARAS, which warrant detailed examination and design of effective therapeutic strategies. Recent randomized clinical trials of renal artery revascularization showed no benefit compared to medical treatment.^{9,11} Among the troublesome results from these studies was an unrelenting high incidence of clinical end-point, implying that more effective strategies of screening, monitoring and treatment are needed in ARAS. While small studies reported that renal revascularization sometimes can reverse accelerated hypertension and restore kidney function, how best to identify these sub-groups and recognize the potentially “viable kidney” remains unknown. To this end, several imaging methods have been developed in an attempt to probe the post-stenotic kidney in ARAS.

This review highlights conclusions gleaned from recent clinical trials and new understanding of ARAS, as well as cutting edge imaging techniques applied for detecting and monitoring ARAS.

Recent clinical trials

Recent randomized clinical trials show that renal artery revascularization does not confer a significant benefit with respect to preservation of kidney function or prevention of adverse renal and cardiovascular events in ARAS patients. Two randomized treatment trials were published in 2009. The Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) and Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trials failed to detect any benefit regarding glomerular filtration rate (GFR) decline, blood pressure (BP), renal function, mortality, or cardiovascular events.^{9,11} The authors concluded that renal revascularization carries substantial procedure-related complications without adding benefit compared to medical treatment. However, these studies have limitations. The ASTRAL study restricted participation to patients in whom the treating physicians was uncertain about the appropriate treatment strategy (patients who would definitely “benefit” from renal revascularization were excluded). In addition, about 40% had a likely non-hemodynamically significant stenosis under 70%. In the STAR trial, among 64 patients allocated to stent therapy, 30% did not undergo revascularization because of non-significant lesion (under 50%) and follow-up loss. These design flaws might have underpowered the results of these trials.

The more recent Cardiovascular Outcomes in Renal Atherosclerotic Lesion (CORAL) study published in 2014 was a large, multicenter, open-label, randomized, controlled trial comparing optimal medical therapy alone to medical therapy plus stenting.¹² CORAL enrolled and followed 947 patients for a median of 43 months. Optimal medical therapy included an angiotensin-receptor blocker (ARB), with or without thiazide-type diuretics, and calcium channel blocker for BP control. Participants also took antiplatelet and a lipid-lowering agent, and some were also randomized to renal revascularization. The rate of the primary composite endpoints, including death and major cardiovascular outcomes, did not differ between medical therapy alone and medical and stenting therapy (35.8% and 35.1%, respectively; hazard ratio, 0.94; 95% confidence interval, 0.76 to 1.17; $p=0.58$). Compared to the medical treatment group, a lower systolic BP was observed in the stented group, but

the number of antihypertensive medications did not differ between the two groups. The authors concluded that renal vascularization with stenting does not have a significant benefit for prevention of clinical events in ARAS patients. However, this well conducted study had some limitations. Enrollment did not require true resistant hypertension. Exclusion criteria precluded patients with recent episodes of congestive heart failure, who might have specifically benefitted from stenting. A recent meta-analysis of several ARAS treatment trials including the CORAL study showed that overall patients receiving endovascular treatment required fewer anti-hypertensive medications, but systolic BP, serum creatinine, and incident cardiovascular event rate were unaffected.¹³ This finding is consistent with the conclusions of previous meta-analyses.^{14,15}

From these studies, it becomes clear that medical treatment should be the preferred management strategy for ARAS patients and that revascularization should be reserved for carefully selected subgroups of patients. However, how to select patients who stand to benefit from stenting is yet a challenge. Clearly, treatment outcomes of medically treated patients remain suboptimal. Furthermore, in recent trials, BP control was aggressive, whereas in real clinical practice, achieving and sustaining optimal BP levels are challenging. Therefore, development of innovative strategies targeting disease mechanisms activated in ARAS is critically needed.

New understanding on the pathogenesis of ARAS

ARAS involves exposure of the post-stenotic kidney to coexisting hypoperfusion, atherosclerosis, and cardiovascular risk factors, which in concert aggravate renal dysfunction and impair kidney architecture. The decline in renal perfusion and function in patients with ARAS does not correlate with the angiographic degree of stenosis,^{16,17} and recent data suggest that its manifestations are far more complex than previously thought. Studies with blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) indicate the kidneys can adapt to substantial reduction in blood flow without developing tissue hypoxia,¹⁸ but extreme vascular compromise overwhelms these adaptations and leads to cortical hypoxia and microvascular injury.¹⁹ Furthermore, regional patches of hypoxia likely develop earlier, but are more difficult to detect.^{20,21} Well established animal models and human studies have clarified the pathogenesis of ARAS distal to the stenosis.^{1,22–24} ARAS not only induces hypoxia in the kidney, but also activates the renin-angiotensin-aldosterone system (RAAS), oxidative stress, inflammation, and microvascular rarefaction, eventuating in kidney failure. (Figure 1)

RAAS activation

The RAAS is one of the major control systems for BP and fluid balance. In a hemodynamically significant stenosis, reduced renal perfusion stimulates release of angiotensin II, which exerts deleterious effects such as oxidative stress, apoptosis, and inflammation.²⁵ In turn, it activates several mechanisms that promote vascular and tissue remodeling. Angiotensin II exerts a strong stimulatory effect on transcription of profibrotic factors like transforming growth factor- β (TGF- β) and plasminogen activator inhibitor-1, leading to accumulation of extracellular matrix. Hence, prolonged activation of angiotensin

II can directly lead to renal fibrosis. Angiotensin II also stimulates nuclear factor- κ B (NF- κ B), leading to activation of inflammatory gene transcription.²⁶ Clinically, RAAS inhibition with either ARB or angiotensin converting enzyme inhibitors (ACEi) has a favorable impact on the kidney, which is thought to be additive to or independent of lowering BP.²⁷ Pharmacological and genetic studies have confirmed that deleterious effects of the RAAS effects are mediated by angiotensin II type-1 receptor (AT1R).^{28–30} ACEi decrease production of angiotensin II, while ARB block AT1R and thereby not only blunt the deleterious effects of angiotensin II, but also allow it to bind to its type-2 receptor (AT2R), which counters the effects of AT1R by inducing vasodilation, anti-proliferation, and anti-apoptosis.²⁵ Moreover, AT2R stimulation in this setting reduces organ damage by both inhibiting arachidonic acid synthesis and limiting activation of NF- κ B.³¹ Recently, we demonstrated that ARBs in a swine ARAS model also preserve the microcirculation of both the kidney³² and heart.³³ The role of angiotensin II in activating the immune system is also under investigation.^{34,35}

Oxidative stress

Much evidence implicates reactive oxygen species (ROS) in the pathophysiology of ARAS.^{24,32,36,37} Oxidative stress, defined as an excessive production of ROS surpassing existing anti-oxidative defense mechanisms, plays a critical role in the development and progression of diabetic vascular complications, including nephropathy.³⁸ Oxidative stress in experimental ARAS has been evidenced by a progressive increase in systemic levels of the oxidative stress markers prostaglandin F₂ α (PGF₂ α)-isoprostanes, associated with decreased endogenous radical-scavenger levels in both the stenotic and contralateral kidneys.²⁴ Activation of the RAAS is also a major determinant of ROS production and may interfere with endogenous adaptive mechanisms of oxidative stress in ARAS.²⁴ Physiologically, a fall in oxygen supply upregulates hypoxia-inducible-factor-1 α and vascular endothelial growth-factor (VEGF) to induce new vessel formation. However, this compensatory capability can be impaired in chronic ischemia by amplified oxidative stress and inflammation.³⁹ ROS also directly increase vascular tone, producing structural and functional impairment in the stenotic kidney, evoking monocyte and lymphocyte infiltration⁴⁰, and hampering the response to revascularization.^{23,41} Indeed, animal experiments showed an ability to reverse these effects using anti-oxidants.^{23,42,43} Notably, several factors account for the consistent failure of human trials to identify a clinical benefit of antioxidants in blunting cardiovascular disease.⁴⁴ First, compared to human cardiovascular disease, animal models are of relatively shorter disease duration and have minimal co-morbidities. Secondly, the benefits of antioxidants might necessitate early administration for successful prevention. Lastly, in many clinical trials, the basal redox status has not been ascertained, and supplementation of subjects without oxidative stress with high-dose antioxidants might paradoxically be harmful.

Inflammation

Mounting data highlight inflammatory cells as important mediators of irreversible kidney damage.^{45,46} Experimental and human studies demonstrate increased release of pro-inflammatory cytokines and decreased anti-inflammatory cytokines in post stenotic

kidneys.^{47,48} Biopsies of human ARAS kidneys identifies altered inflammatory cell populations,^{49,50} and renal vein samples reveal multiple markers such as tumor necrosis factor (TNF)- α , interferon- γ , interleukin (IL)-6 and neutrophil gelatinase-associated lipocalin (NGAL), reflecting active inflammation.^{47,48} These observations are supported by previous studies indicating elevated systemic levels of TNF- α and IL-6 in patients²² and pigs⁵¹ with renovascular hypertension. TNF- α has been implicated in renal inflammation by inducing expression of cell adhesion molecules, monocyte chemoattractant protein (MCP-1), IL-1, IL-6, and IL-8.⁵² In experimental renovascular disease, upregulated expression of MCP-1 in the stenotic kidney was accompanied by inflammatory cell infiltration,⁴⁰ and MCP-1 blockade decreased inflammation and fibrosis and improved renal function and microvascular density.

In contrast to activation of pro-inflammatory pathways, anti-inflammatory mechanisms are downregulated in ARAS. Renal vein levels of the anti-inflammatory cytokine IL-10 are decreased in ARAS patients compared with essential hypertension and healthy volunteers.⁴⁷ Furthermore, a recent study demonstrated increased number of M1 (pro inflammatory) and decreased number of M2 (reparative) macrophages in the post stenotic swine kidney.³⁷

Interestingly, renal injury and inflammation within the ARAS kidney persist after revascularization despite reversal of hypoxia. In patients with ARAS, stent revascularization failed to decrease inflammatory markers such as NGAL, MCP-1 and TNF- α ,⁵³ which might be linked to the failure to improve renal function compared to medical treatment.

Taken together, these findings underscore the important role of inflammation and the innate immune system in the pathogenesis of ARAS.

Fibrosis

Ongoing inflammation and hypoxia stimulate production and activity of growth factors that modulate renal tissue response to ischemia, like collagen deposition, extracellular matrix turnover, fibrosis, and defective angiogenesis.^{54,55} Excessive matrix accumulation finally leads to renal fibrosis, which in turn promotes irreversible damage and loss of functioning nephrons, a major pathological feature of progressive kidney disease.⁵⁶ Renal fibrosis is observed in experimental and clinical ARAS, associated with vascular remodeling and microvascular rarefaction.^{36,50,57} TGF- β has long been considered a key mediator in renal fibrosis and induces renal scarring. A major rise in TGF- β was observed in the post-stenotic kidney of mice,⁵⁸ and in human kidney biopsies, increased tissue TGF- β was accompanied by CD68+ macrophage infiltration.⁵⁰ TGF- β mediates progressive renal fibrosis by stimulating extracellular matrix accumulation and inhibiting matrix metalloproteinases (MMP),^{59,60} likely mediated through its small-mother-against-decapentaplegic (Smad)-3 effector.⁶¹ In addition, recent studies have implicated the p38-MAPK pathway in development of renal inflammation and fibrosis.^{62,63} Several stimuli, including angiotensin II, ROS, TNF- α , IL-1 and TGF- β , activate p38 to induce renal damage, and its blockade attenuates renal atrophy and fibrosis in stenotic murine kidneys.⁶³ Therefore, treatments targeting these pathways might prevent irreversible kidney damage.

Microvascular rarefaction

Patients with ARAS exhibit intra-renal microvascular disease leading to vascular rarefaction.^{50,57} Prolonged periods of reduction of renal blood flow, and increased inflammation, endothelial dysfunction, oxidative stress, and fibrosis can alter the microcirculation, most prominently inducing microvascular remodeling (e.g., thickening) and rarefaction (reduced number or combined length).^{36,64} In an experimental swine model, 3D micro-computed tomography images obtained from the stenotic kidney of ARAS confirm significant impairment of microvascular architecture and spatial density (Figure 2). Although inflammatory mediators stimulate angiogenesis in early disease,⁵⁴ new vessels may be highly permeable, allowing inflammatory cells to migrate to the interstitium, thereby aggravating renal parenchymal injury. In addition, microvascular remodeling correlates with renal fibrosis,⁶⁵ which constrains vascular growth and increases tortuosity.³⁶ Consequent microvascular rarefaction aggravates renal damage and compromises renal functional outcomes after revascularization.³

New imaging techniques of ARAS

The diagnosis of ARAS often relies on imaging studies. The CORAL study enrollment criteria included Duplex Doppler Ultrasonography velocity above 300 cm/sec, with computed tomography (CT) or magnetic resonance (MR) angiography stenosis greater than 60% in one or both renal arteries.¹² Because these criteria do not necessarily reflect the degree of injury in the renal parenchyma, these techniques merely evaluate the stenosis and macro-anatomy of the kidney. However, the severity of parenchymal injury is an important determinant of renal outcomes in ARAS.¹⁷ Recently emerging novel imaging tools show promise for evaluation of post-stenotic circulation and function. These might also provide individualized and unique information to stratify patients who might benefit from revascularization, medical treatment only, or new developing treatment strategies such as regenerative therapy.

Multi Detector Computed Tomography (MDCT)

During the past decade, CT angiography has become a standard noninvasive imaging modality for exploration of renal vascular anatomy and pathology. Moreover, newer applications of CT also provide reliable assessment of functional parameters of kidney function such as renal blood flow (RBF), GFR, and tubular dynamics of each kidney^{4,66} by recording changes in renal tissue image density, which is consequent to transit of a bolus of contrast media in the kidneys.^{4,67} CT derived GFR and RBF correlated with measurements obtained by intravascular Doppler and inulin clearance.⁴ In patients undergoing stenting, renal revascularization improved CT-measured cortical and medullary RBF and perfusion, whereas GFR remained unchanged.⁵³ Because quantitative functional measurements can be obtained during routine clinical examination, MDCT could provide valuable functional information. However, CT is limited by the need for contrast media and by the radiation burden.

BOLD-MRI

BOLD-MR imaging is a unique noninvasive tool capable of monitoring changes in intrarenal oxygenation. The endogenous contrast agent in BOLD-MRI is paramagnetic deoxyhemoglobin, which accelerates signal decay (shortens $T2^*$) as its concentration increases, and reciprocally increases the BOLD index, $R2^*$ ($1/T2^*$), which correlates with tissue hypoxia (Figure 3).⁶⁸ Studies in a swine model confirmed a linear relationship between measurement of renal $R2^*$ by BOLD-MRI and direct measurements of pO_2 levels in the renal tissue using oxygen sensitive microelectrodes.^{69,70} Furthermore, BOLD-MRI can estimate the renal oxygen-dependent functional reserve using diuretics that inhibit oxygen-dependent transport and increase oxygenation. The post-stenotic pig kidney shows increased hypoxia and reduced furosemide-induced suppression of oxygen-consumption.⁷¹

Can BOLD-MRI be useful in ARAS patients? In patients with a moderate unilateral ARAS, interestingly, cortical and medullary $R2^*$ did not differ from those in patients with essential hypertension,⁷² but the fall in $R2^*$ after furosemide was blunted in stenotic compared to contralateral kidneys. Furthermore, kidneys with severe stenosis had elevated $R2^*$,¹⁸ and calculation of “fractional kidney hypoxia” with BOLD-MRI demonstrated direct relationship to RBF and GFR.⁷³ Therefore, kidneys can adapt to moderate reduction in blood flow without tissue hypoxia, but have functional impairment, whereas a more severe stenosis produces cortical hypoxia associated with vascular rarefaction.

While unquestionably powerful, application of BOLD-MRI is not routine in ARAS and the complex processes that define $R2^*$ require careful interpretation. For example, a recent study showed that BOLD-MRI failed to discriminate patients with various stages of chronic kidney disease.⁷⁴ Factors such as differences in hematocrit, fibrosis, and oxygen-dependent transport activity may all affect the BOLD signal. Clearly, this technique warrants further investigation, as it may allow the clinician to quantify the severity of renal dysfunction in ARAS and predict its recovery.⁷⁵

Magnetic Resonance Elastography (MRE)

MRE is an emerging MRI modality that can noninvasively quantify and visualize tissue elasticity⁷⁶ using an imaging-based counterpart to palpation, commonly used in physical examination. ARAS induces CKD characterized by under-perfusion of the kidney and tissue scarring due to tubulointerstitial fibrosis.⁴⁵ Renal biopsy is too invasive to employ routinely, and is not representative of the entire kidney due to sample size limitation. The main advantage of MRE is its noninvasiveness and sampling the entire kidney. Our group demonstrated that acute decreases in swine RBF without development of fibrosis led to a fall in renal cortical stiffness in a swine model.⁷⁷ Consequently, in chronic renal artery stenosis, the stiffness of the stenotic cortex was unchanged despite the presence of fibrosis confirmed by histology. Presumably, a decrease in RBF offsets an increase in stiffness secondary to development of renal fibrosis. MRE of kidney allografts supported this finding.⁷⁸ Contrarily, 3-dimensional MRE detected increased medullary stiffness in ARAS kidneys,⁷⁶ which correlated with the histological degree of fibrosis and could potentially be used to track

longitudinal ARAS progression. However, further studies are needed to examine the utility of this promising approach in humans with ARAS.

Treatment

All patients with ARAS should implement life style modification (e.g., smoking cessation, exercise, etc.) and medical treatment to prevent disease progression and complications.

Medical treatment

Hypertensive patients with ARAS should be treated with antihypertensive medications. Despite past controversy, ACEi and ARB seem to be well tolerated and effective, unless patients have contraindication to their use. Appropriate laboratory monitoring of kidney function and electrolytes while on therapy is prudent. Moreover, addition of thiazide diuretics, calcium channel blockers, and beta-blockers may be necessary to reach the target BP. The target levels of BP in the CORAL study were under 140/90 mmHg for patients without coexisting conditions and under 130/80 mmHg for patients with diabetes or chronic kidney disease.¹² Current guidelines recommend BP goals of <150/90 mmHg for the general population 60 years or older, and under 140/90 mmHg for younger individuals.⁷⁹ The optimal BP target for patients with ARAS has not been established. The use of statins, antiplatelet drugs, and diabetic medications is pivotal for preventing complications.

Revascularization

Although revascularization is not superior to medical treatment for BP control and prevention of cardiovascular complications, medical regimens may fail in some patients. In high-risk patients with ARAS, who were likely excluded in previous trials, revascularization should be considered. High-risk clinical presentations include recurrent episodes of heart failure or sudden unexplained pulmonary edema, acute or sub-acute kidney injury due to ACEi or ARB therapy, resistant renovascular hypertension, and rapid kidney function decline.⁸⁰

Novel Treatment Strategies

Recent studies have applied cell-based therapies and novel drugs to the treatment of ARAS. Intra-renal administration of endothelial progenitor cells stimulates proliferation and maturation of new vessels, and attenuates renal microvascular remodeling and fibrosis in an experimental model.^{5,81} Furthermore, delivery of endothelial progenitor cells at the time of revascularization blunts inflammation and improves renal function recovery.³⁷ Similarly, administration of adipose tissue-derived mesenchymal stem cells into the stenotic kidney restores the renal microcirculation by suppressing inflammatory cytokines and apoptosis, normalizes renal function, and decreases renal fibrosis.⁸²

Endothelin-1 receptor blockers⁸³, and angiogenic factors like VEGF⁸⁴ or hepatocyte growth factor⁸⁵, also confer renoprotective effects in the stenotic kidney. Finally, protection of mitochondria in ARAS with mitochondrial-targeted peptides preserves tissue integrity and improves hemodynamics and function in the post-stenotic kidney.^{43,86}

Conclusion

ARAS remains an important cause of CKD, but the mechanisms underlying kidney injury in this disease have not been fully elucidated. Several pathophysiologic mechanisms have been implicated and targeted for treatment in ARAS, but clinical outcomes remain suboptimal. Current management in patients with ARAS includes antihypertensive drugs, risk factor modification, and revascularization. However, given the potential renal and cardiovascular complications, newer therapeutic interventions are needed, such as new drugs, gene, and cell-based therapies. Importantly, novel imaging tools may assist in early detection and monitoring of renal parenchymal injury and viability distal to ARAS.

Acknowledgments

Funding source: This article was partly supported by NIH grants DK73608, DK104273, HL121561, and DK100081.

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Clinical summary

- Despite intensive treatment, a substantial number of patients with atherosclerotic renal artery stenosis progress to have renal and cardiovascular events.
- The complex pathogenesis of atherosclerotic renal artery stenosis warrants therapeutic interventions targeting atherosclerosis, hypoxia, and inflammation.

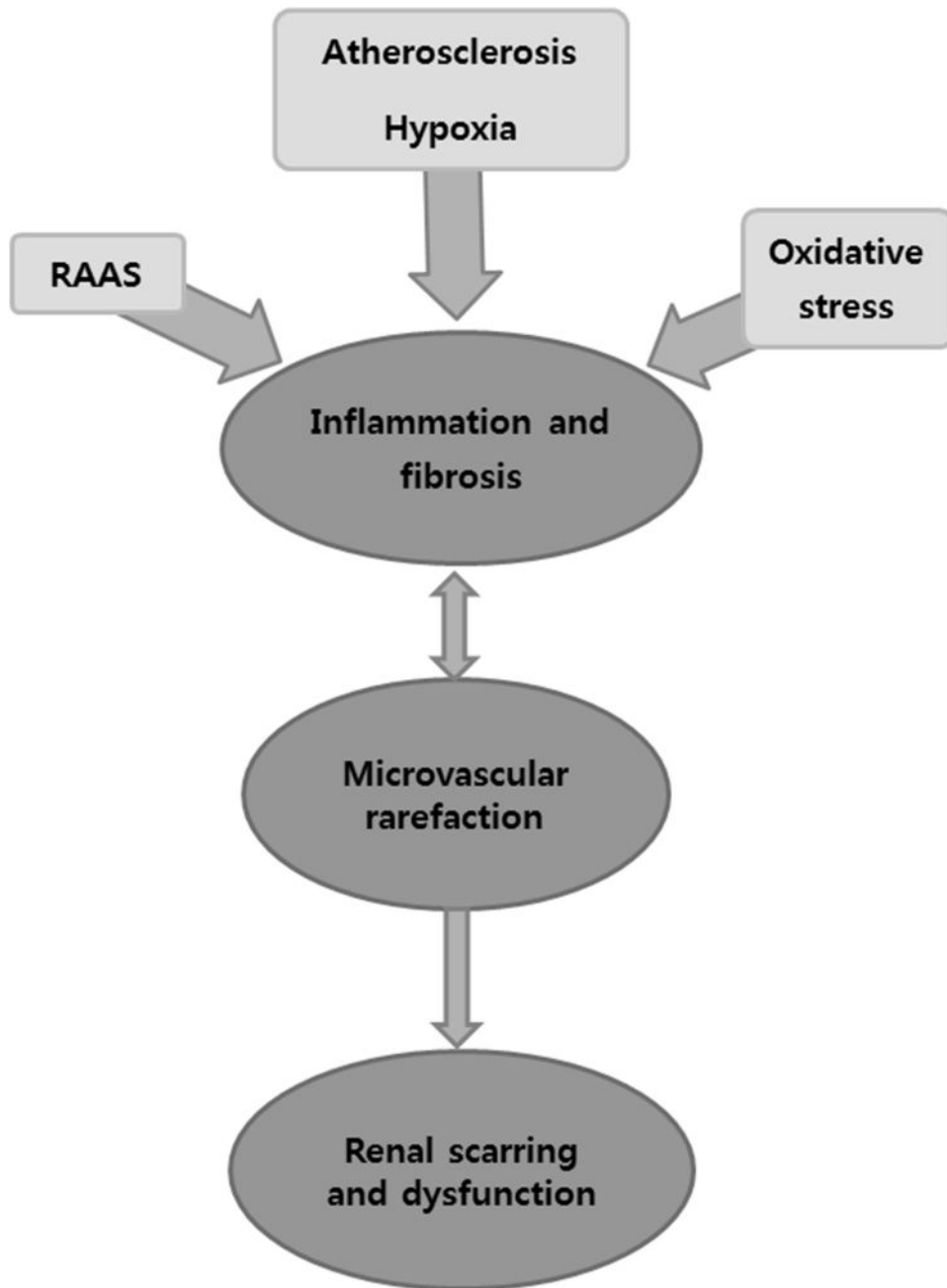


Figure 1.

Schematic of interactive mechanisms responsible for kidney injury in atherosclerotic renal artery stenosis (ARAS). A critical renovascular occlusion activates the renin-angiotensin-aldosterone system (RAAS), elicits hypoxia, and increases oxidative stress. Together with atherosclerosis this process induces parenchymal inflammation, fibrosis, microvascular loss, and kidney dysfunction.

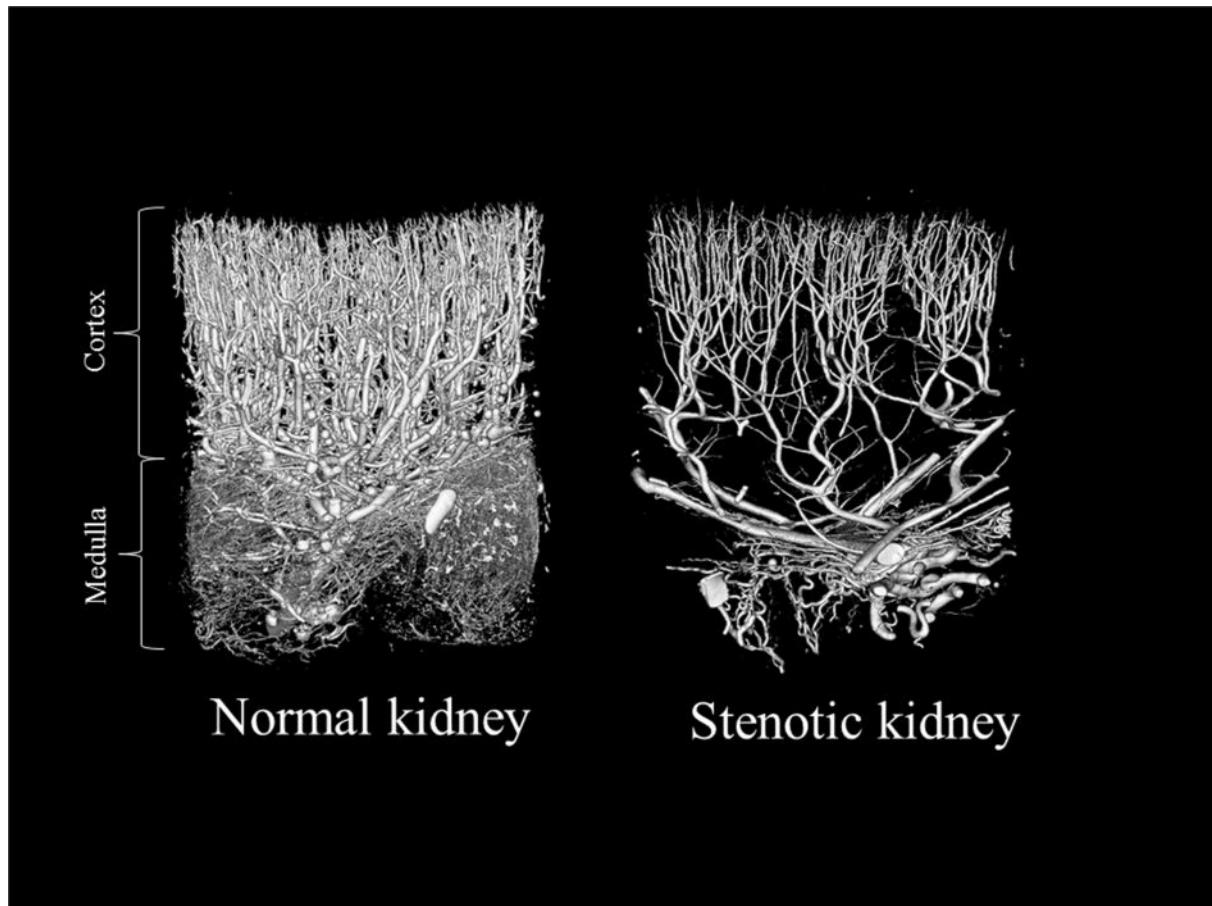


Figure 2. Representative 3D micro-computed tomography images from a normal (left) and a stenotic swine kidney, showing a decreased number of cortical and medullary microvessels in the hypo-perfused kidney.

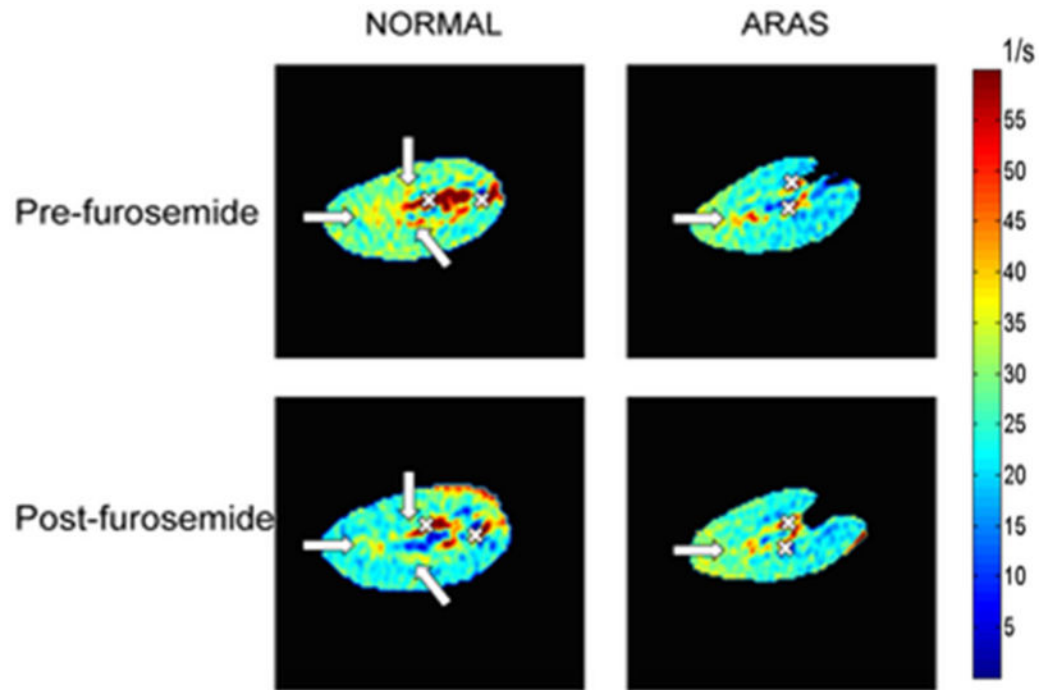


Figure 3. Blood oxygen-level-dependent (BOLD) parametric map in normal pigs (left) and in a swine model of atherosclerotic renal artery stenosis (ARAS) (right) obtained before and after injection of furosemide, which inhibits oxygen-dependent tubular transport and thereby increases kidney oxygenation. Arrows indicate the medullary regions, and crosses blood vessels. Medullary R2* was higher (more red) both at baseline and after furosemide in ARAS, suggesting greater hypoxia and blunted response to furosemide compared to normal pig kidneys.