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Novel Therapeutic Strategies for Renovascular Disease

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Abstract

Purpose of review: Renovascular disease (RVD) remains an important cause of hypertension and renal dysfunction. Given the failure of renal revascularization to provide consistent clinical benefit in the Cardiovascular Outcomes for Renal Artery Lesions (CORAL) trial among others, further research has underscored the need for mechanistically targeted interventions to improve renal outcomes in patients in RVD. This review discusses novel therapeutic approaches for RVD in the post-CORAL era.

Recent Findings: Emerging evidence indicates that renal inflammation, microvascular remodeling, and mitochondrial damage accelerate progression of renal injury and are important determinants of the response to revascularization. Experimental studies have identified interventions capable of ameliorating renal inflammation (e.g. cytokine inhibitors, mesenchymal stem cells), microvascular remodeling (pro-angiogenic interventions), and mitochondrial injury (mito-protective drugs), alone or combined with renal revascularization, to preserve the structure and function of the post-stenotic kidney. Recent prospective pilot studies in patients with atherosclerotic RVD demonstrate the safety and feasibility of some of such interventions to protect the kidney.

Summary: Experimental studies and pilot clinical trials suggest that therapies targeting renal inflammation, microvascular remodeling, and mitochondrial damage have the potential to preserve the structure and function of the stenotic kidney. Further studies in larger cohorts are needed to confirm their renoprotective effects and clinical role in human RVD.

Keywords

renovascular disease; hypertension; inflammation; mitochondria; microvasculature

Introduction

Renovascular disease (RVD) due to atherosclerotic lesions in the renal artery remains an important cause of secondary hypertension and renal failure in the aging population (1, 2). Patients with RVD tend to progress to chronic kidney disease and have an increased risk for developing renovascular hypertension (RVH) and cardiovascular complications, increasing morbidity and mortality (3).

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Conflict of Interest

None

While restoring renal artery patency by revascularization would seem to be a logical approach to preserve the renal parenchyma beyond a stenotic lesion, results from clinical trials fail to demonstrate consistent recovery of post-stenotic kidney function. Two randomized clinical trials, the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) (4) and Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) trials (5) concluded that compared with medical therapy, revascularization carries some substantial risk, without adding benefit with respect to renal function.

Cooper and colleagues published the results of the Cardiovascular Outcomes for Renal Artery Lesions (CORAL) trial in 2014 (6). In this multi-center, randomized, controlled trial, patients with atherosclerotic RVD were randomly assigned to medical therapy plus percutaneous transluminal renal angioplasty (PTRA) or medical therapy alone. After a median follow-up of 43 months, renal revascularization failed to confer incremental benefit over conventional medical therapy with respect to prevention of clinical cardiovascular events and renal dysfunction. Taken together with the conclusions of a Medicare and Medicaid review panel (7), such outcome results reduced selection of patients for renal revascularization. The number of PTRA/stenting procedures for atherosclerotic RVD has fallen in recent years (8). It has become clear that restoring blood flow to the chronically ischemic kidney does not by itself predictably restore renal function. Renal revascularization procedures are currently reserved for patients with severe and progressive RVD.

An important corollary to these observations has been to emphasize the importance of research efforts directed to better define the main determinants of the response to renal revascularization and to develop novel interventions to improve renal outcomes (9). A major paradigm shift in RVD is the understanding that the natural history of the disease involves transition from a hemodynamic component to a pro-inflammatory and pro-fibrotic disease (10). While early RVD is characterized by reduction in renal blood flow (RBF), activation of inflammatory and pro-fibrotic pathways can subsequently produce significant renal damage not directly related to the degree or hemodynamic impact of stenosis. Therefore, extensive parenchymal injury, including inflammation, fibrosis, and microvascular remodeling, imparts irreversible injury in the post-stenotic kidney.

Several studies in recent years have tested the efficacy of interventions to attenuate renal inflammation and preserve microvascular integrity or renal mitochondrial structure and function in RVD. This mini-review briefly discusses these therapeutic approaches for RVD in the post-CORAL era. None have yet been approved for routine clinical use. Studies in both animal models and human subjects have been summarized in order to highlight the potential of these interventions to ameliorate parenchymal injury and foster tissue repair in RVD.

Anti-inflammatory interventions

Several lines of evidence have shown that inflammation markedly aggravates renal dysfunction in experimental RVD. We have shown in post-stenotic swine kidneys increased

expression of pro-inflammatory cytokines, such as chemokine monocyte chemoattractant protein (MCP)-1 (11) and tumor necrosis factor- α (12), associated with inflammatory cell infiltration and renal dysfunction (13). Data from renal biopsies and nephrectomy specimens from patients with RVD, characterized by macrophage infiltration and fibrosis (14), support these observations. Furthermore, renal vein blood from post-stenotic swine (15) and human (16) kidneys contains multiple active inflammatory biomarkers associated with episodes of acute kidney injury and reduced function (17). Importantly, release of pro-inflammatory cytokines inversely correlates with renal functional recovery after PTRa (15), underscoring the dominant role of inflammation in determining response to renal revascularization in RVD.

In light of these observations, therapies targeting inflammation-related pathways have emerged as novel interventions to preserve the structure and function of the post-stenotic kidney (11). MCP-1 inhibition in swine RVD improves post-stenotic RBF, glomerular filtration rate (GFR), and endothelial function (11), and attenuates left ventricular hypertrophy and diastolic dysfunction (18). Therefore, blunting renal inflammation could potentially introduce a therapeutic target in RVD and hypertensive cardiomyopathy.

Likewise, mesenchymal stem cells (MSCs), which possess important immunomodulatory and anti-inflammatory properties, ameliorate post-stenotic injury and recover function in swine and murine models of RVD (19, 20). Renal subcapsular delivery of autologous MSCs improves renal morphology and reduces fibrosis in a 2-Kidneys 1-Clip model (21). Similarly, intra-arterial delivery of adipose tissue-derived MSCs ameliorates post-stenotic injury in swine RVD (22, 23). These beneficial effects are partly mediated by modulation of inflammatory pathways, including inducing a macrophage phenotype shift from inflammatory (M1) to reparative (M2) populations (24).

Additionally, intra-arterial MSC delivery during PTRa restores stenotic-kidney function, reduces inflammation (25), and improves medullary oxygenation (26) after revascularization in swine, supporting the reno-protective properties of this anti-inflammatory intervention. The observation that MSC delivery with and without PTRa also decreases myocardial remodeling and improves cardiac function in swine RVD (27, 28) suggests a therapeutic potential for MSCs in blunting systemic complications of chronic experimental RVH.

Importantly, many of these findings were recently confirmed in a pilot clinical trial. Intra-arterial infusion of autologous adipose tissue-derived MSCs was safe and well tolerated in patients with atherosclerotic RVD without revascularization, and associated with increased cortical perfusion and RBF 3 months later (29). Furthermore, renal vein levels of pro-inflammatory cytokines tended to decrease after MSC therapy, underscoring the potential of anti-inflammatory cell therapy to preserve the post-stenotic human kidney (30).

MSCs achieve repair by paracrine mechanisms, including release of growth factors and extracellular-vesicles (EVs) (31, 32). MSC-derived EVs carry several anti-inflammatory genes (33) and proteins (34, 35). Intra-renal delivery of EVs decreases renal inflammation and injury in experimental RVD (36, 37). However, these beneficial effects are abolished in EVs depleted of interleukin-10, supporting its contribution to EV function (37). Taken

together, these observations suggest that anti-inflammatory interventions can ameliorate injury and preserve function in the post-ischemic kidney. Additional experimental and clinical trials with longer follow-up periods are warranted to confirm their safety and long-term clinical efficacy in RVD.

Therapies to restore the renal microcirculation

Microvascular remodeling and rarefaction are important determinants of renal dysfunction in RVD, and may compromise renal outcomes after revascularization. Inflammation, oxidative stress, and fibrosis all damage the structure and function of the renal microvasculature, potentiating renal damage (38). Tortuous and leaky vessels in turn permit extravasation of inflammatory mediators and infiltration of inflammatory cells into the interstitium.

Microvascular remodeling and loss also impair renal perfusion and amplify tissue hypoxia, aggravating renal parenchymal injury and impairing functional recovery after PTR. Indeed, the number of small outer cortical microvessels correlates directly with GFR in swine RVD (39). Remodeling of intra-renal vessels also correlates with progressive deterioration of perfusion, RBF, and tubular function (40, 41).

RVD-induced changes in the renal microvasculature are frequently associated with decreased expression of angiogenic factors, including vascular endothelial (VEGF) and hepatocyte (HGF) growth factors (42). These factors participate in microvascular protection, repair, and proliferation, and deficiency in their renal expression likely reflects “defective angiogenesis” that aggravates stenotic kidney microvascular damage (42). Targeted interventions that preserve or promote proliferation of the renal microvasculature have been postulated to attenuate injury and improve renal function in RVD.

Indeed, intra-renal delivery of VEGF increases angiogenic signaling and preserves the microvasculature in swine RVD (40). Furthermore, its delivery combined with PTR improves microvascular density and renal function (43), consistent with the premise that microvascular disease determines responses to revascularization in experimental RVD. Similarly, intra-renal HGF improves RBF and GFR in the swine stenotic kidney (44). However, high concentrations of these compounds in the kidney are often needed, increasing the likelihood of side effects (45). In addition, RVD-induced changes in glomerular filtration and tubular function may compromise the distribution of these drugs to the kidney.

Selective targeting of the kidney may increase the efficacy of pro-angiogenic factors and minimize extra-renal side effects. In swine RVD, systemic biopolymer-stabilized, elastin-like polypeptide (ELP)-delivered VEGF promotes therapeutic angiogenesis in the post-stenotic kidney (46, 47). Furthermore, longer plasma half-life and higher renal selectivity can be achieved by modifying ELP with a seven-amino-acid, kidney-targeting peptide (KTP) and a cysteine residue (48). Therefore, kidney-specific delivery methods can minimize extra-renal side effects and enhance drug efficacy, providing functional recovery in RVD.

Regenerative therapy with endothelial progenitor cells (EPCs) and MSCs may also preserve and/or repair the microvasculature in animal models of renal disease. These cells express and secrete VEGF and may incorporate into vascular structures (27, 49), so that intra-renal

delivery of EPCs (22, 49–52) or MSCs (24, 25) restores the post-stenotic kidney microcirculation and function in experimental RVD. Furthermore, these cells can blunt pathways that contribute to microvascular damage, including oxidative stress, apoptosis, inflammation, and development of fibrosis. Development of techniques to deliver reparative cells to the kidney cells using targeting or “homing” signals may allow systemic (intravenous) administration and expedite clinical translation of this approach (53).

Recent studies in swine RVD have shown that six sessions of low-energy external ultrasonic shockwave (SW) increase microvascular density and alleviate renal dysfunction distal to a stenosis (54, 55). This mechanical stimulus upregulates renal expression of pro-angiogenic pathways (56, 57), improving the ischemic kidney microcirculation. Importantly, this novel therapy does not cause detectable kidney injury in normal pigs, underscoring its safety (54). A recent pilot study in patients with diabetic nephropathy reported safety of SW therapy in human kidneys as well (58). Further studies are needed to define the optimal regimen of SW treatment in the ischemic kidney.

Mitoprotective drugs

A growing body of evidence implicates renal mitochondrial dysfunction in the pathogenesis of tissue damage associated with RVD (59). One of the mechanisms involved may include activation of angiotensin-II type-2 receptors in the inner mitochondrial membrane (60), which stimulate production of mitochondrial reactive oxygen species (ROS) (61, 62) and induce apoptosis of renal tubular cells (63). Angiotensin-II also increases cytosolic ROS, favoring oxidation of mitochondrial lipids and proteins (64), and mitochondrial-DNA mutations (65). This may in turn prevent transcription of mitochondrial proteins implicated in ATP synthesis and respiration (66). ROS can also trigger the formation of the mitochondrial permeability transition pore, and release of cytochrome-c and mitochondrial ROS to the cytosol (67, 68), contributing to apoptosis and cellular oxidative stress (69). Extracellular matrix accumulation can directly damage mitochondria and promote apoptosis (70). Hence, mitochondrial damage and dysfunction compromise overall cell functioning, instigating a progressive cycle of mitochondrial injury and cellular damage in RVD.

The mitoprotective drug elamipretide (ELAM) prevents oxidation of the mitochondrial inner membrane phospholipid cardiolipin and formation of the mitochondrial permeability transition pore, and exerts important reno-protective effects in several models of kidney injury. We have shown that ELAM attenuates stenotic-kidney microvascular loss and injury, and improves oxygenation, hemodynamics, and function in pigs with RVD (71). Furthermore, adjunctive ELAM during renal reperfusion attenuates microvascular rarefaction (Figure 1) and structural damage, and improves renal function 4 weeks later (12). ELAM also attenuated left ventricular remodeling and preserved diastolic function in swine RVD (72, 73), underscoring its capability to ameliorate RVH-induced cardiomyopathy.

Notably, delivery of ELAM before and during renal artery stenting in human RVD attenuated post-procedural hypoxia, increased RBF, and improved GFR (74). Infused systemically, this adjunctive intervention is noninvasive and clinically feasible. Therefore,

targeted mitochondrial protection might minimize procedure-associated ischemic injury and improve outcomes after PTRa.

Other reno-protective strategies

Additional noteworthy interventions include antioxidants, endothelin-1 blockers, angiotensin-II inhibitors, and statins. Increased oxidative stress in the stenotic kidney is blunted by antioxidant vitamins (75), which decrease inflammation and fibrosis, and restore microvascular architecture (76). Alas, they paradoxically increase oxidative stress in healthy pigs (77), which may limit their widespread use. Endothelin-A receptor blockade preserves function and microvasculature in the stenotic kidney (78), and enhances functional recovery after PTRa in swine RVD (79).

Agents that block the renin-angiotensin system (RAAS) and cholesterol lowering therapy with statins define optimal management of patients with RVD. Both angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin-receptor-blockers (ARBs) have been associated with long-term mortality benefits compared to other antihypertensive drugs (80, 81). The CORAL study found that ACEi and ARBs were well-tolerated, and patients treated with these drugs before enrollment were likely to achieve blood pressure goals at the end of the study (82). Although these drugs reduce filtration pressures and may acutely decrease post-stenotic kidney GFR, their beneficial tissue effects are superior to triple-therapy. Indeed, treatment with valsartan for 4 weeks not only decreased blood pressure, but also stimulated microvascular density and improved tubular function in swine RVD (83).

Statins are also known for pleiotropic effects, and may slow progression of post-stenotic kidney injury in human RVD by decreasing oxidative stress, endothelial dysfunction, and tissue fibrosis (84). We have also shown in swine RVD that chronic simvastatin supplementation ameliorates stenotic-kidney microvascular remodeling (85), and prevents apoptosis of endothelial progenitor cells, underscoring their potential to preserve renal repair mechanisms (86), independent of lipid-lowering. Therefore, these observations support the early use of RAAS blockers and statins in patients with RVD. Lastly, dampening pro-fibrotic pathways like transforming growth factor- β /Smad3 signaling may also decrease kidney scarring (87), and thereby protect the kidney in RVD.

Conclusions and perspectives

For many years, management of patients with RVD was based primarily on the assumption that restoring renal artery patency would improve renal function. However, disappointing results from several clinical trials have undermined this assumption and led to a dramatic reduction in clinical revascularization. Notwithstanding, these observations have magnified the importance of research to define the mechanisms of irreversible renal injury and develop novel therapies to improve renal outcomes in these patients. Anti-inflammatory, pro-angiogenic, and mitoprotective interventions have emerged as powerful strategies and showed promising results in experimental RVD, particularly in conjunction with renal revascularization.

Importantly, the safety and potential efficacy of several of these novel interventions have been validated in pilot clinical trials in patients with atherosclerotic RVD. Notably, the effects of these strategies to protect and/or restore renal function may be independent of reversing the effect of RVD on blood pressure regulation. Ultimately, their roles likely will be adjunctive when combined with selective restoration of blood flow to the affected kidneys. Further studies are warranted to establish their clinical role as a multipronged approach for preservation and recovery of renal function in human clinical RVD.

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KEY POINTS

- Atherosclerotic renovascular disease remains an important cause of renal failure in the elderly population.
- Compared with medical therapy, revascularization carries some substantial risk, without adding benefit with respect to renal function.
- The natural history of the disease involves transition from a hemodynamic component to a pro-inflammatory and pro-fibrotic disease.
- Renal inflammation, microvascular remodeling, and mitochondrial damage accelerate progression of renal injury and are important determinants of the response to revascularization.
- Therapies targeting these pathways have potential to preserve the structure and function of the stenotic kidney.

Figure 1.

Representative 3D micro-computer tomography images showing that treatment with percutaneous transluminal renal angioplasty (PTRA) and elamipretide (ELAM) increased the number of cortical and medullary microvessels in the swine stenotic-kidney.