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Renovascuclar Disease: Mechanisms of its Poor Cardiovascular response to Revascularization

Eirin A and Zhang X*

Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

***Corresponding author:** Zhang X, Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA, Tel: (507)-286-2069; Fax: (507)-266-9316; **E-mail:** zhang.xin@mayo.edu

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Renal artery stenosis (RAS) is caused by narrowing of the renal artery which supplies the downstream kidney. The etiologies of RAS vary with atherosclerosis being the most common, accounting for approximately 90% of the lesions that obstruct blood flow to the renal arteries [1]. Atherosclerotic RAS (ARAS) typically involves the ostium and/or proximal one-third of the renal artery and often the adjacent aorta. It could affect one or both kidneys.

The prevalence of ARAS, like coronary artery disease and other atherosclerotic vascular lesions, increases with advancing age and with the presence of traditional cardiovascular risk factors such as age, hyperlipidemia, smoking, diabetes, and overweight/obesity. The degree of obstruction deteriorates over time, compromising post-stenotic kidney function. Indeed, a prospective study revealed that ARAS accounts for 14% of patients with end-stage renal disease in whom dialysis was newly initiated [2].

Importantly, patients with ARAS develop renovascular hypertension, which not only accelerates renal injury, but also strongly associates with cardiovascular complications. Due to subsequent and persistent activation of renin-angiotensin-aldosterone system, the blood pressure is elevated and can affect the heart, leading to myocardial infarction, left ventricular hypertrophy, heart failure, and even pulmonary edema [3]. Indeed, the presence of ARAS is known to predict adverse coronary events and mortality [4,5]. It can also affect the peripheral vasculature causing blood vessel remodeling and atherosclerosis, as well as the brain causing stroke [3].

Current treatment options for patients with ARAS include medical therapy (anti-hypertensive and lipid-lowering drugs) and renal revascularization. Restoration of vessel patency by percutaneous transluminal renal artery stenting (PTRAS) is a common interventional strategy for these patients, but its capability to preserve renal function remains controversial and only selected groups of patients benefit. Large clinical trials such as the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) [6] and the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trials [7] failed to demonstrate significant benefits for recovery of renal function beyond medical therapy alone. Furthermore, in a meta-analysis, PTRAS did not show benefit in improvement of renal function, nor did all-cause mortality, congestive heart failure, or stroke rates decline during the 29-months follow-up, underscoring the need to identify more effective strategies to treat these patients [8].

Over the last couple of decades, accumulating evidence has demonstrated that multiple injury pathways are activated beyond a stenotic lesion. Importantly, these pathways play a critical role in the progression of kidney and cardiovascular damage. Studies have shown that ARAS is associated with elevated systemic levels of markers of oxidative stress [9,10] and inflammation [11]. We have previoulsy shown that farm pig with RAS is associated with increased systemic levels of isoprostanes and renal expression of oxidative stress markers, such as nitrotyrosine [12]. In addition, macrophages infiltrate the stenotic kidney and release multiple inflammatory cytokines such as tumor necrosis factor-α and monocyte chemoattractant protein-1, which subsequently enter the systemic circulation. Finally, recent studies from our group have shown mitochondial abnormalities and impaired myocadium energy metabolism in swine ARAS, implicating mitochondrial dysfunction in the pathogenesis of RAS-induced cardiac damage [13,14]. Taken together, these findings support the clinical observation that simply restoring renal artery patency cannot fully recover tissue damage, and treatment therapies that block these pathways may attenuate hypertension and progressive renal dysfunction in ARAS. Understanding how these pathways are activated and how interact with each other, could help us to get more insight into the pathogenesis of ARAS and also to develop novel therapeutic interventions to target these pathways to attenuate progressive renal injury and dysfunction in ARAS.

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