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Revascularization in Experimental Atherosclerotic Renal Artery Stenosis: Role of Mitochondrial Targeted Peptides (Bendavia)

Alfonso Eirin* and Lilach O Lerman

Department of Internal Medicine, Divisions of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Atherosclerotic Renal Artery Stenosis (ARAS) is a common cause of secondary hypertension, especially in the elderly population, and is often associated with increased cardiovascular morbidity and mortality, as well as progression to chronic renal insufficiency [1,2]. Consequently, treatment options have been increasingly directed towards the preservation of renal function and reduction in the progression to end-stage renal disease (ESRD).

Antihypertensive drug therapy with angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin II receptor blockers (ARBs) is extensively used for controlling blood pressure, and at times for salvaging the function of the ischemic kidney [3]. This approach is supported by several studies that suggested considerable survival advantages for patients treated with these drugs [4,5]. However, restoring blood flow is critical for specific individuals such as those with progressive decline in renal function during antihypertensive treatment or inadequate blood pressure control after optimal medical therapy [6].

The procedure of choice for revascularization in ARAS is percutaneous transluminal renal angioplasty and stent implantation (PTRS). Although small clinical trials demonstrated the potential of PTRS for lowering blood pressure and improving renal function in ARAS [7,8], several major prospective clinical studies have reported no measureable clinical benefit from revascularization compared to medical therapy alone [9,10]. Likewise, our group has previously shown in a swine model of ARAS that PTRS failed to improve tubulointerstitial injury, microvascular rarefaction, and renal function four weeks after treatment, despite correction of the stenosis (normal blood pressure levels) [11]. This might be linked to ongoing tissue damage distal to the stenois that is not relieved by revascularization. Taken together, these observations emphasize the need for adjunctive therapies to improve renal outcomes after revascularization in ARAS.

Considerable evidence implicated mitochondrial dysfunction as an important mechanism in sustaining tissue injury after revascularization. Increased inflammation and oxidative stress at the time of reperfusion may compromise mitochondrial function, leading to cell death by apoptosis. For example, increased production of reactive oxygen species (ROS) may cause cardiolipin peroxidation in the inner mitochondrial membrane, triggering the formation of the mitochondrial permeability transition pore (mPTP) [12]. This may in turn facilitate the release of cytochrome C into the cytoplasm and initiation of apoptosis [13]. Therefore, therapies focused on preventing oxidative injury in the mitochondria might be associated with better outcomes after revascularization.

Mitochondrial targeted aromatic-cationic peptides, originally designed by Szeto and Schiller, are small water soluble synthetic peptides (less than 10 amino acids) that concentrate in the inner mitochondrial membrane and prevent formation of the mPTP [14]. Experimental studies in rats have shown that pretreatment with these peptides reduced myocardial lipid peroxidation and infarct size in ischemia-reperfusion injury [15]. Among them, Bendavia (also known as SS-31) has shown unique antiapoptotic and antioxidant properties in several disorders associated with significant ROS generation, such as ischemia reperfusion injury [14,16]. Furthermore, treatment with Bendavia ameliorated hypertension-induced cardiomyopathy in mice by preventing angiotensin II-induced oxidative stress [17], underscoring its potential role in the prevention of hypertensive cardiovascular diseases.

Recently, experimental studies have illustrated unique Reno protective effects of Bendavia for attenuating tissue injury and improving renal function in different experimental models. For example, infusion of Bendavia 30 minutes before bilateral occlusion of renal blood flow for 30-45 minutes reduced medullary vascular congestion, decreased oxidative stress and inflammation, and accelerated the proliferation of surviving tubular cells in a rat model of ischemic kidney injury [18]. Similarly, Mizuguchi et al. demonstrated that pretreatment of rats with Bendavia decreased renal damage and oxidative stress in a model of unilateral ureteral obstruction [19]. In line with these observations, we have recently shown in swine ARAS that systemic infusion of Bendavia during the PTRS procedure (from 30min before to 3.5 hours after PTRS), promoted renal mitochondrial biogenesis and attenuated microvascular remodeling, apoptosis, oxidative stress, tubular damage, and fibrosis evaluated four weeks after revascularization [20]. Furthermore, renal inflammation, one of the main determinants of disease progression and response to revascularization in ARAS [21], was restored to normal levels in Bendavia-treated pigs. Remarkably, stenotic-kidney blood flow and glomerular filtration rate were normalized in animals treated with Bendavia, suggesting a unique potential of this drug for limiting renal reperfusion injury in chronic experimental ARAS.

In summary, restoration of function to the kidney by renal angioplasty in ARAS has not been supported by clinical studies, warranting development of alternative protective strategies in combination to PTRS to preserve renal structure and function in the stenotic kidney. The evidence available from the studies reviewed above reveals that mitochondrial targeted peptides like Bendavia possess cardio and Reno-protective properties in experimental models of ischemia reperfusion injury. Our recent findings suggest potent anti-apoptotic and antioxidant effects of Bendavia for improving the efficacy of PTRS in chronic experimental renovascular disease. Future studies are needed to examine the feasibility of this approach in human ARAS.

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***Corresponding author:** Lilach O. Lerman, MD, PhD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905. E-mail: Lerman.Lilach@Mayo.Edu

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