Potential Cardiometabolic Benefits of Renal Artery Denervation in Diabetics

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Abstract

Treatment of hypertension using renal artery sympathetic denervation was first reported as early as 1924, [1] but only recently has the advent of safer, less invasive techniques allowed this treatment modality to emerge as a promising treatment for hypertension [2-4]. Aside from reductions in blood pressure, the effect of this treatment appears to be more widespread than initially thought. Renal artery sympathetic denervation may globally reduce cardiovascular risk through a variety of mechanisms such as decreased insulin resistance, oxidative stress, and organ hypertrophy, along with improvement in diastolic function and other metabolic parameters [5-11]. The following is a comprehensive review of current literature on renal artery sympathetic denervation with a focus on potential cardiovascular benefits.

Keywords: Renal artery denervation; Hypertension; Cardiovascular risk; Hypertension; Diastolic function

Introduction and Pathophysiology

Renal artery denervation for treatment of hypertension was first reported in 1924 using surgical sympathectomy to control malignant hypertension [1]. In 1953, over 1200 cases were reported in which splanchnectomy was used to control essential hypertension [12]. After decades, recent clinical investigation has reported catheter based renal sympathetic denervation for treatment of essential hypertension [2]. Together, these studies have shown that renal artery sympathetic denervation can effectively lower blood pressure, highlighting the potential use of sympathectomy in the clinical treatment of hypertension. With the advent of safer, minimally invasive catheter-based techniques, the field of renal sympathetic denervation is emerging as a welcome addition to the armamentarium used to simultaneously modify multiple risk factors that globally reduce cardiometabolic risk.

An improvement in cardiovascular risk profile is at least partially attributable to reduced sympathetic mediated release of circulating adrenaline and local tissue norepinephrine. Catecholamine release can directly lead to tissue insulin resistance and promote development of type 2 diabetes [13]. Reducing sympathetic nerve activity via denervation results in decreased catecholamine release which may improve insulin mediated metabolic effects described. Furthermore, sympathetic activation increases adipose tissue lipolysis leading to increased circulating free fatty acids that have important effects on insulin action in heart, muscle and liver [7]. At a more cellular level, insulin resistance is linked to oxidative stress related to higher levels of reactive oxygen species from dysfunctional mitochondrial respiration [8,14]. Increased inflammation and adipokine dysregulation also accompany sympathetic activation [15]. Cumulatively, increased sympathetic drive promotes insulin resistance associated with increased aortic stiffness, hypertension, sodium retention, blood volume, hyperlipidemia, and thrombogenicity, resulting in a vascular milieu that heightens atherothrombotic risk [6,16,17]. These factors interact with a vulnerable vascular wall to further elevate cardiovascular risk in the hypertensive patient [18].

Aside from alterations in hormonal and metabolic regulation, sympathetic denervation directly impacts renal autonomic regulation of blood pressure. The autonomic regulation of renal physiology is predominantly sympathetic and it has been extensively studied [19-21]. The kidney has a dense post-ganglionic network of sympathetic neurons which when activated, directly release norepinephrine onto granular juxtaglomerular cells, which in turn, release renin. At low levels, this “spillover” of norepinephrine results in increased renin release, while at higher levels, it results in greater sodium retention and reduced renal blood flow via vasoconstriction of vascular smooth muscle [19,22,23]. Overall, increased norepinephrine spillover contributes to hypertension via activation of the renin-angiotensin system, vasoconstriction, and sodium retention. Studies of Dahl sensitive rats found that greater renal sympathetic activation was linked to increased hypertrophy and growth, suggesting that renal sympathtics play a role in gross structural change and remodeling as well [24]. These gross findings were consistent with evidence of growth and hypertrophy from stimulation of alpha-1 adrenergic receptors with norepinephrine in cellular studies [25]. More recent data has suggested that renal sympathetic denervation may result in not only decreased blood pressures, but also a reduction in left ventricular hypertrophy, perhaps more clearly linking the aforementioned mechanisms with a gross, tangible endpoint [5].

In summary, renal artery denervation primarily reduces sympathetic activation, which decreases catecholamine release, altering metabolic effects of insulin, as well as autonomic regulation of blood pressure. Through multiple sympathetic-mediated mechanisms, denervation can lower blood pressure and wall stress, as well as improve metabolism of lipids, insulin resistance and thrombogenicity [26,27] (Figure 1). The above changes may result in a gross decrease in ventricular hypertrophy and global cardiovascular risk [9]. Reducing sympathetic nerve activity could result in not only significant global risk reduction, but also the greatest absolute risk reduction in all-cause mortality without oral medications, highlighting an adjunctive and
While the full details of assessing diastolic dysfunction are outside the scope of this review, it is an evolving process and parameters assessed include left a trial size, mitral valve inflow pattern, hepatic vein flow, pulmonary venous flow, and tissue Doppler imaging (TDI) (Figure 2). A relatively new echocardiographic technique, tissue Doppler imaging enhances diagnostic potential through increased sensitivity for detection of early diastolic dysfunction [31]. This modality measures relative velocities of the mitral annulus (e') and mitral inflow (E) during diastole (Figure 1) [32]. In a recent study of more than 1700 patients with diabetes mellitus, 23% had pre-clinical manifestations of diastolic dysfunction by TDI. After adjusting for demographics, cardiovascular risk factors, and echocardiographic parameters, pre-clinical diastolic dysfunction was associated with subsequent development of heart failure. The presence of diastolic dysfunction in diabetic patients more than doubled the cumulative probability of heart failure at 5 years compared to diabetic patients with normal diastolic function (36.9% vs. 16.8%, p < 0.001). Diabetic patients with diastolic dysfunction also had significantly higher cumulative mortality rates at 1 and 5 years compared to those without diastolic dysfunction (6.9% vs. 3.1% at 1 year; 30.8% vs. 12.1% at 5 years) (Figure 3) [33].

In additional cohort studies, diabetes and hypertension were independently associated with diastolic dysfunction after adjusting for multiple covariates including age, heart rate, and left ventricular mass, geometry, and ejection fraction [34]. Interestingly, longer duration of diabetes mellitus (11-15 years), higher HbA1c (>7.5%), presence of autonomic neuropathy and retinopathy, as well as increased waist circumference have also positively correlated with increased incidence of diastolic dysfunction [35]. While the mechanism of this association remains unclear, it is well known that diabetic patients have increased risk of myocardial steatosis, which is frequently coupled with diastolic dysfunction and increased cardiovascular risk. Lending credence to this theory, one study demonstrated that diastolic strain rate and myocardial perfusion reserve (by cardiac magnetic resonance imaging) were significantly impaired in patients with type 2 diabetes mellitus compared to age-matched healthy control subjects. Even in the absence of coronary artery disease, this impairment correlated with diastolic dysfunction and myocardial triglyceride content [36].

Whether or not myocardial steatosis fully explains the increased prevalence of diastolic dysfunction in diabetic patients, it is clear that competitive strategy for cardiovascular risk reduction (Table 1). The following sections represent a more extensive clinical review of renal artery denervation including cardiovascular benefits with a focus on diabetes, limitations of current data, and technical aspects.

**Diastolic Function in the Diabetic Patient**

Diastolic dysfunction in asymptomatic patients is associated with increased risk of clinical congestive heart failure and cardiovascular morbidity and mortality [28]. While not clearly understood, the existence of diabetic cardiomyopathy was initially proposed based on postmortem findings in 1972 [29]. Since then, both systolic and diastolic abnormalities in diabetic subjects in addition to increased microangiopathy, extracellular collagen deposition, and reported abnormalities in calcium transport have been postulated as possible mechanisms of cardiomyopathy [30].

Echocardiography is widely used to assess diastolic dysfunction.
Comparing important cardiovascular risk factor treatment options, reveals the potential of renal artery denervation as one treatment that may have many benefits in reducing cardio-metabolic risk. However, risk to patient with renal artery denervation must be further evaluated with large trials for safety and long term concerns.

Table 1: Strategies for cardiovascular global risk reduction.

| Study Name | Location | Enrollment | Design | Purpose | Primary Outcome(s) |
|------------|----------|------------|--------|---------|--------------------|
| DENER-HTN  | France   | April 2012 | multi-center, open label RCT | RD + conventional medical therapy v. medical therapy alone | Mean ambulatory BP, cost effectiveness |
| Renal Denervation in patients with advanced heart failure | Turkey | April 2012 | observational | Test improvement in ventricular function and functional capacity after RD in advanced heart failure population | Safety measured by MACE |
| Global SYMPLICITY registry | Germany | Feb 2012 | open label, multi-center registry | Document 5- year safety and efficacy profile from minimum 5000 patients at 200 centers; data collection diabetes, CHF, CKD | Long-term BP measurements after RD in relation to sympathetically driven diseases |
| DREAMS | Netherlands | Nov 2011 | observational | Test efficacy of RD on insulin resistance in metabolic syndrome | Decrease in insulin resistance after 12 months |
| Renal Denervation in patients with chronic heart failure and renal impairment | Australia | Oct 2011 | observational | Feasibility study of RD in heart failure patients with renal dysfunction | Safety measured by MACE |
| PRAGUE-15 | Czech Republic | Oct 2011 | observational | RD + conventional medical therapy v. medical therapy alone (5 years) | Decrease in office BP, MACE |
| SYMPLICITY HTN-3 | United states | Sept 2011 | multi-center, single blind RCT | Test efficacy and safety of RD in refractory hypertension on a large scale | Decrease in office BP after 6 months |
| ReSET | Denmark | Sept 2011 | single-center, multi blind RCT | Test efficacy of RD in improving ambulatory blood pressure | Ambulatory BP change at 3 months |
| Renal sympathetic modifications in patients with metabolic syndrome | China | Aug 2011 | observational | Measure effects of RD on cardio-vascular events , glucose and lipid metabolism | Composite MACE |
| Renal nerve ablation in chronic kidney disease patients | Germany | Nov 2010 | observational | Evaluate and understand pathogenesis of RD in the CKD population | Ambulatory BP, renal perfusion , Na+ excretion, RAS activity, vascular structure and function |
| Combined treatment of resistant hypertension and atrial fibrillation | Greece | April 2010 | observational | RD + PVI v. PVI alone to reduce AF recurrence | BP lowering, freedom from AF |

Table 2: Upcoming Renal Denervation Trials.

| RD: Renal Denervation |
|-----------------------|
| BP: Blood Pressure |
| CHF: Congestive Heart Failure |
| CKD: Chronic Kidney Disease |
| PVI: Pulmonary Vein Isolation |
| AF: Atrial Fibrillation |
| MACE: Major Adverse Cardiovascular Events |

These are the most recent updated renal denervation trials.
elevations in both normal weight patients with essential hypertension and in obesity-related hypertension [38]. This may in many patients increase cardiac after load from skeletal muscle vasconstriction which could significantly increase cardiovascular risk. These associations place this group of patients as one of the highest for a new myocardial infarction or stroke from the INTERHEART and INTERSTROKE trial. Is it possible renal artery denervation would be especially helpful in this high risk group. From many perspectives renal artery denervation may perhaps reduce wall stress and sympathetic drive that are two of the most important risk factors for plaque fracture in high risk metabolic patients. It is only speculative at this point and clearly requires much more investigation.

**Pulse Wave and Central Aortic Pressure Change in the Diabetic Patient**

Central aortic pressure directly measures the load seen by the heart, and more specifically, the left ventricle. Changes in arterial stiffness are recorded as an increase in central aortic pressure. Increased central aortic pressure correlates on a pathophysiologic level with cardiovascular disease [39]. Physiologically, a marked difference between peripheral and central aortic pressure occurs as the pressure wave travels away from the heart and to the peripheral vascular system. As mean and diastolic blood pressure decrease, there is an increase in systolic blood pressure, resulting in an increased pulse pressure (difference between systolic and diastolic pressure). Aging and atherosclerosis increase arterial stiffness, which is also influenced by arterial wall composition, smooth muscle tone and endothelial derived mediators such as nitric oxide (NO). Diabetic patients are well known to have increased vascular stiffness as evidenced by increased central aortic pressure [40].

Due to highly variable amplification of pressure between the aorta and the brachial artery in subjects, central blood pressure is a better predictor of cardiovascular risk. In a recent study, central systolic blood pressure and augmentation index (a measure of enhancement by a reflected pulse wave) were independent predictors of new onset diabetes mellitus in 12.4% of 178 patients with essential hypertension followed over 2 years [41].

Pharmacologic treatment to reduce arterial stiffness has been historically limited to statins and peroxisome proliferator-activated receptor (PPAR) agonists [42,43]. These agents are particularly beneficial for individuals with diabetes and metabolic syndrome [17]. Catheter-based renal denervation results in a significant decrease in systolic and diastolic blood pressure (32 mmHg and 12 mmHg, respectively) with concomitant reductions in fasting glucose (118 to 108 mg/dL), insulin levels, and glucose levels after 2 hour oral glucose tolerance testing [10]. Based on these initial results, current studies are in progress to further evaluate the direct effects of catheter-based renal denervation on central aortic pressure, pulse waveforms, and cardiometabolic variables [44]. These results and further study are necessary to determine the effect of renal denervation on arterial stiffness and cardiometabolic factors as they relate to total cardiovascular risk.

**Limitations of Current Renal Denervation Studies**

At present, the multiple positive effects of catheter-based renal denervation as an adjunct therapy for medically-refractory hypertension are very promising. As mentioned, in addition to improvement in blood pressure, the resulting sympathetic inhibition impacts neurohormonal regulation and insulin sensitivity in the diabetic population. However, it remains premature to conclude that renal denervation can result in true disease regression. The initial Simplicity HTN-1 trial was a small observational cohort study aimed to demonstrate efficacy and evaluate safety of catheter-based renal artery nerve ablation. Limitations of the
pooled subgroup data is largely positive at 6 months (Figure 4), longer based blood pressure measurements at 6 months [3]. Though initial when compared to home (20/12 mmHg) and office (33/11 mmHg) pressure was seen in 24 hour ambulatory monitoring (11/7 mmHg) possible white coat syndrome. A smaller overall reduction in blood and 24 hour blood pressure measurements were used to exclude resistant hypertension. At 2 years, renal denervation effects on blood study included lack of randomization and a control group along with office blood pressure measurement and treatment being limited to resistant hypertension. At 2 years, renal denervation effects on blood pressure were durable, but long-term follow up data was limited to a small population of only 18 patients [4].

The Simplicity HTN-2 trial overcame some of these limitations via a randomized, controlled design to evaluate 100 patients. Ambulatory and 24 hour blood pressure measurements were used to exclude possible white coat syndrome. A smaller overall reduction in blood pressure was seen in 24 hour ambulatory monitoring (11/7 mmHg) when compared to home (20/12 mmHg) and office (33/11 mmHg) based blood pressure measurements at 6 months [3]. Though initial pooled subgroup data is largely positive at 6 months (Figure 4), longer term follow up of larger numbers of patients is still needed to evaluate durability of results and the possible applicability of the treatment to patients with less severe hypertension.

While we await more data on the effects of renal denervation in subgroups such as patients with diabetes, animal studies have demonstrated that hyperinsulinemia is sympathetically driven and linked to hypertension, but interestingly, not to metabolic syndrome. In fact, in denervated rats, there were no changes in levels of insulin, triglyceride, random blood glucose, weight, or urinary sodium excretion, when compared to controls [45]. Further clinical investigation in humans will be helpful in reconciling this discrepant data.

Finally, while small numbers of patients have demonstrated durable changes in blood pressure after denervation, the possibility of renervation may decrease the sustainability of renal denervation and raise the specter of rebound hypertension. The persistence of denervation after transplant and nephrectomy may not apply to catheter-based nerve ablation. Post-denervation neural re-growth has not been established, but studies of this technique and its long-term effects are in early stages. Multiple studies are under way to better evaluate the safety and efficacy of catheter-based renal denervation in multiple contexts and better address these limitations of early trials (Table 2).

**Technical Aspects and Complications of Catheter-Based Renal Denervation**

Early methods of sympathetic renal denervation were limited to surgical approaches associated with high perioperative morbidity and mortality, including profound postural hypotension, as well as bowel, bladder and erectile dysfunction. The retroperitoneal location of the kidneys additionally increases the technical difficulty of surgical sympathectomy. Given these obstacles, recently developed catheter-based techniques offer a novel approach to renal denervation to reduce sympathetic drive (Figure 5) [46].

Percutaneous endovascular ablation of the renal sympathetic nerves begins with establishing traditional access via the femoral artery for a retrograde approach to the renal arteries. After placement of a 6 Fr sheath, diagnostic bilateral renal angiography may be performed. At the discretion of the operator, pre-procedural non-invasive imaging (renal duplex, CT, MRI) or pre/intra-procedural abdominal aortography can be utilized for evaluating anatomic eligibility and as a guide for catheter selection and engagement [3,47]. Recent trial protocols have excluded patients with vascular abnormalities including significant renal artery stenosis, prior renal artery stenting or angioplasty, and dual renal arteries [2]. Commonly used catheters for engaging the renal arteries include the internal mammary, hockey stick, Judkin’s right or renal double-curve catheters [48]. Upon engaging the right or left renal artery with the appropriate guiding catheter using standard interventional techniques, a specially designed catheter (SymplicityTM, Medtronic, and Mountain View, California) is advanced to the distal renal artery. Trial protocols have included the administration of heparin to achieve an activated clotting time of more than 250 seconds. Subsequently, serial radiofrequency (RF) ablations are performed in 2-minute intervals. The steerable catheter is pulled back and rotated in order to deliver additional RF energy via a generator at a total of 4-6 discrete locations, ultimately resulting in a spiral pattern of ablation along the length of the renal artery. A predetermined algorithm for the generator monitors catheter tip temperature and impedance to regulate RF energy delivery. The ablations are typically repeated in the contralateral renal artery.

Figure 5: The illustration above shows both renal arteries with angiographic catheter. The diagram below demonstrates the use of radiofrequency catheter to ablate the renal artery nerves on the outside wall of the renal artery.

Figure 6: This figure shows a birds eye view of the potential of renal artery sympathetic nerve ablation but there are significant risks to the renal artery that need to be addressed from research and clinical trials. Trading hypertension control for renal artery damage or no blood pressure benefit would not be a good outcome for most patients.
artery and upon completion, the catheter is straightened and removed [3,46,49,50].

Procedural complications to date have been limited to risks typically associated with any endovascular procedure including infection, bleeding, and vascular access complications. As with any procedure, myocardial infarction (MI), cerebrovascular accident (CVA), renal failure, arrhythmia, hypotension, and death are risks as well. However, to date, there have been no significant, immediate complications related to the ablation itself. Renal artery dissections and complications have been attributable to engagement of the renal arteries rather than delivery of the ablation catheter and/or RF energy. Pain associated with RF ablation of the renal sympathetic nerves has been suggested as a potential marker of successful denervation, but remains fortunately short-lived and easily controlled [2,3,49,51].

Summary

In summary, catheter-based renal denervation offers a novel, minimally invasive, and simple approach to renal sympathectomy with minimal immediate peri-procedural risks and a multitude of cardiovascular benefits in addition to blood pressure control: improved insulin sensitivity, lipid profile, left ventricular hypertrophy, and diastolic function. While early data is positive, this new potential therapy requires further clinical study and extended follow up to better evaluate long-term risks and benefits (Figure 6).

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