Journal of Diabetes and Metabolism
ISSN: 2155-6156
Maraj et al. J Diabetes Metab 2012, S:3
DOI: 10.4172/2155-6156.S3-007
Review Article
Open Access

Potential Cardiometabolic Benefits of Renal Artery Denervation in Diabetics

Suraj Maraj[1], Rikesh Patel[1], Rene Oliveros[2]*, Saurabh Sanon[1], Tim Dao[1], Sik Hur[1] and Robert Chilton[1,2]

[1]*Division of Cardiology, The University of Texas Health Science Center at San Antonio, USA*
[2]*Division of Cardiology, The University of Texas Health Science Center at San Antonio and Janey Briscoe Center of Excellence for CV Research, San Antonio, USA*

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 splanchiectomy 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 mileu 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 salt sensitive rats found that greater renal sympathetic activation was linked to increased hypertrophy and growth, suggesting that renal sympthatics 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

***Corresponding author:** Oliveros Rene, Division of Cardiology, The University of Texas Health Science Center at San Antonio and Janey Briscoe Center of Excellence for CV Research, San Antonio, USA, E-mail: oliveros@uthscsa.edu

Received May 23, 2011; **Accepted** July 06, 2012; **Published** July 11, 2012

Citation: Maraj S, Patel R, Oliveros R, Sanon S, Dao T, et al. (2012) Potential Cardiometabolic Benefits of Renal Artery Denervation in Diabetics. J Diabetes Metab S3:007. doi:10.4172/2155-6156.S3-007

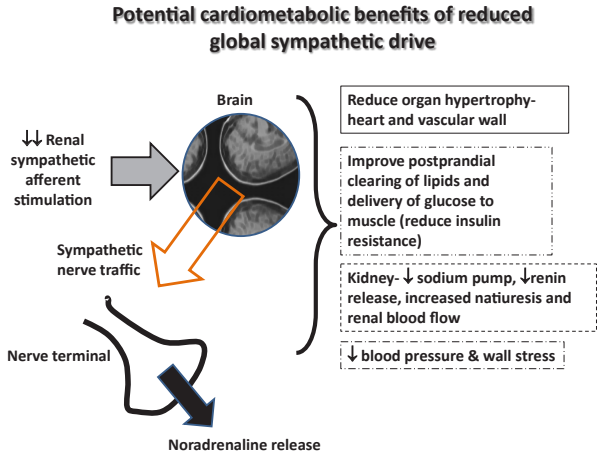


Figure 1: Sympathetic nervous system when activated increases release of noradrenaline (manifested by increased sympathetic nerve traffic—this is organ and regionally specific). The reduced activation from renal artery denervation has the potential to reduce multiple key cardiovascular risk factors in one treatment. The circulation levels of noradrenaline have been correlated with increased mortality from numerous trials over the last 20 years (53).

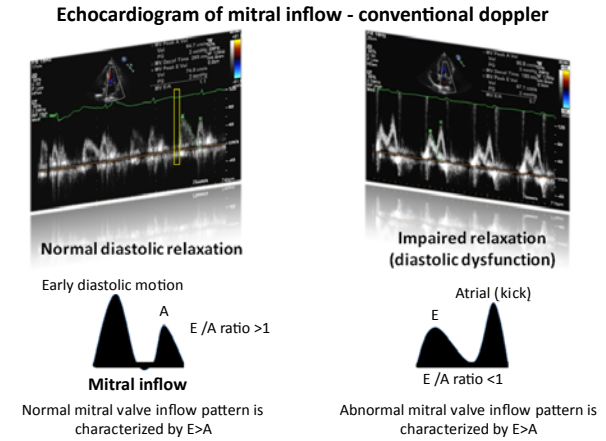


Figure 2: This figure compares normal echocardiographic diastolic relaxation to impaired relaxation of diastolic dysfunction.

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. 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% v. 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% v. 3.1% at 1 year; 30.8% v. 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

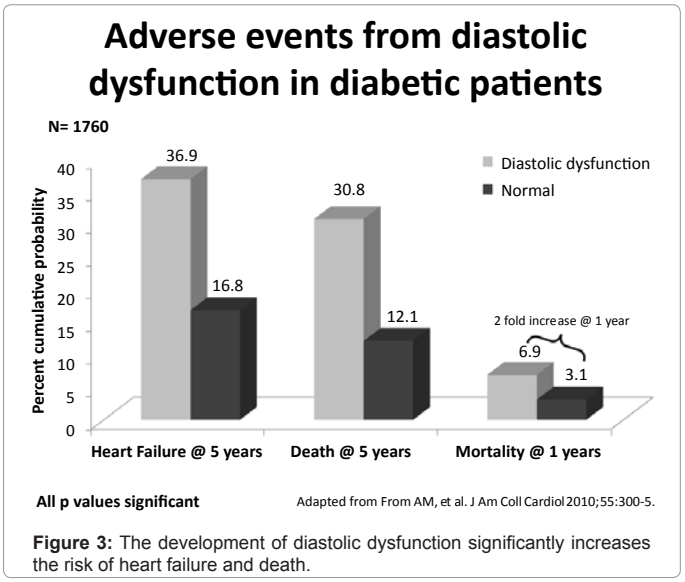


Figure 3: The development of diastolic dysfunction significantly increases the risk of heart failure and death.

	Hyperlipidemia	Abnormal obesity	Smoking	HT	Diabetes	Stress	Number of treatments	Risk benefits
Renal artery denervation	Benefit triglycerides & HDL slight	No	No	YES	Reduces Insulin resistance	Unknown	1	Risk of vascular damage- no further treatment
Drug treatments	Yes No mortality for ↓ triglycerides	Maybe	Maybe	YES with mortality data	No primary endpoint CV mortality data	Maybe in patients after MI	6 different drugs	Lifelong therapy

HT: Hypertension
HDL: High Density Lipoprotein
CV: Cardiovascular
MI: Myocardial Infarction

Adapted from INTERHEART; Juni P, et al. Lancet 2004; 364: 2021-9

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 cardiovascular 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

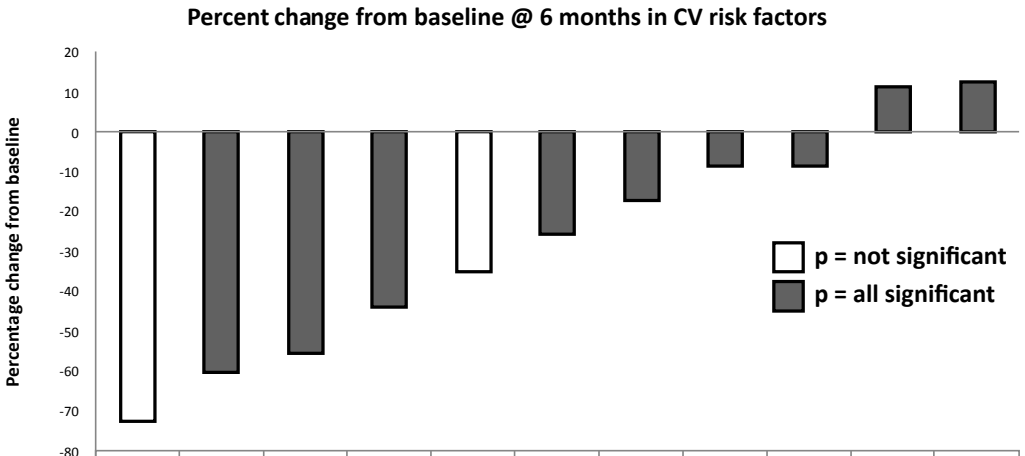
RD: Renal Denervation
BP: Blood Pressure
CHF: Congestive Heart Failure
CKD: Chronic Kidney Disease
PVI: Pulmonary Vein Isolation
AF: Atrial Fibrillation
MACE: Major Adverse Cardiovascular Events

These are the most recent updated renal denervation trials

Table 2: Upcoming Renal Denervation Trials.

even pre-clinical diastolic dysfunction is associated with increased cardiovascular risk in terms of heart failure and mortality. Recent data from a subgroup analysis from the Symplicity-HTN-2 trial suggests that renal sympathetic denervation may offer a treatment to offset this significant risk. In 46 patients who underwent bilateral catheter-based renal artery denervation, 2-dimensional transthoracic echocardiography at baseline, 1 and 6 months, demonstrated significant, continued reduction in LV mass and marked improvement in LV diastolic function. The control group which did not receive renal artery denervation had increased LV mass and decline in diastolic function. In addition to reductions in systolic and diastolic blood pressure, the renal denervation cohort also had decreased levels of pro-B-type natriuretic peptide, which is often a marker of left ventricular function [5]. Renal artery denervation may offer a unique method of improving diastolic function and cardiac remodeling in patients with severe, refractory hypertension, though the direct clinical significance of these potential benefits require further study.

In closing, one of the highest risk group's physician's faces is the patient with type 2 diabetes, hypertension and metabolic syndrome. There is increased sympathetic outflow to the skeletal muscle vasculature, which is accentuated when hypertension, obesity, and metabolic syndrome co-exist [37]. Renal norepinephrine spillover recordings from sympathetic nerve fibers have shown up to three-fold



	Apnea-hypopnea index (events/hr)	Insulin resistance (HOMA-IR)	serum insulin (µIU/ ml)	c-peptide (ng/mL)	BNP (ng/L)	LVEDP (lateral E/E')	LVH (g/m 2.7)	fasting glucose (mg/dL)	HgbA1c (%)	EF(%)	Insulin sensitivity (IS QUICKI)
% Change	-72.4	-60	-55.3	-43.4	-35.3	-25.3	-17	-8.5	-8.2	11.1	12.5

Data adapted from:
Esler MD, et al. Lancet 2010;376:1903-9.
Brandt MC, et al. J Am Coll Cardiol 2012;59;901-9.
Mahfoud F, et al. Circulation 2011;123:1940-6.
Witkowski A, et al. Hypertension 2011;58:559-65.

Figure 4: This figure illustrates the potential benefit of renal artery denervation on many important risk factors.

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 vasoconstriction 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

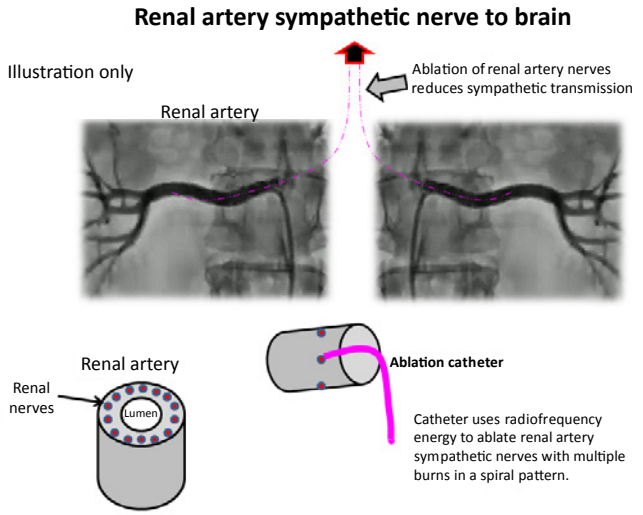


Figure 5: The illustration above shows both renal arteries with angiographic catheter. The diagram below demonstrates the use of radiofrequency catheter to ablate the renal artery nerves on the outside wall of the renal artery.

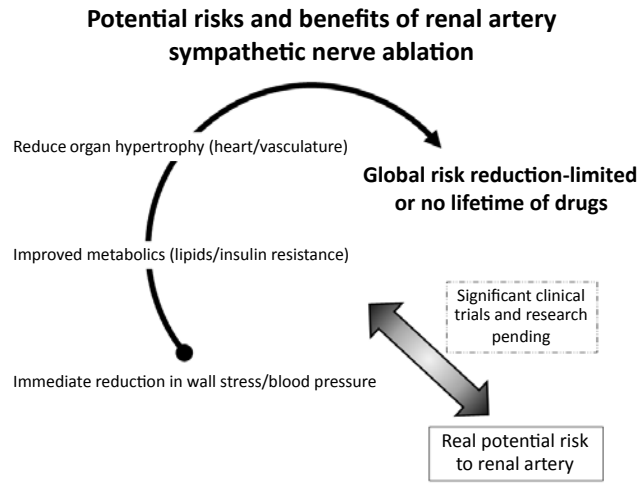


Figure 6: This figure shows a birds eye view of the potential of renal artery sympathetic nerve ablation but there are significant risks to the renal artery that need to be addressed from research and clinical trials. Trading hypertension control for renal artery damage or no blood pressure benefit would not be a good outcome for most patients.

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 their 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 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 treatment for hypertension requires further clinical study and extended follow up to better evaluate long-term risks and benefits (Figure 6).

References

1. Smithwick RH (1949) An evaluation of the surgical treatment of hypertension. Bull N Y Acad Med 25: 698-716.
2. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, et al. (2009) Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 373: 1275-1281.
3. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. (2010) Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 376: 1903-1909.
4. Symplicity HTN-1 Investigators (2011) Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension 57: 911-917.
5. Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, et al. (2012) Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol 59: 901-909.
6. Bruno RM, Penno G, Daniele G, Pucci L, Lucchesi D, et al. (2012) Type 2 diabetes mellitus worsens arterial stiffness in hypertensive patients through endothelial dysfunction. Diabetologia 55: 1847-1855.
7. Buren J, Eriksson JW (2005) Is insulin resistance caused by defects in insulin's target cells or by a stressed mind? Diabetes Metab Res Rev 21: 487-494.
8. Evans JL, Maddux BA, Goldfine ID (2005) The molecular basis for oxidative stress-induced insulin resistance. Antioxid Redox Signal 7: 1040-1052.
9. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, et al. (2004) Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 364: 2021-2029.
10. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, et al. (2011) Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation 123: 1940-1946.
11. Witkowski A, Prejbisz A, Florczak E, Kądziela J, Śliwiński P, et al. (2011) Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension 58: 559-565.
12. Smithwick RH, Thompson JE (1953) Splanchnicectomy for essential hypertension; results in 1,266 cases. J Am Med Assoc 152: 1501-1504.
13. Jamerson KA, Julius S, Gudbrandsson T, Andersson O, Brant DO (1993) Reflex Sympathetic Activation Induces Acute Insulin Resistance in the Human Forearm. Hypertension 21: 618-662.
14. Houstis N, Rosen ED, Lander ES (2006) Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature 440: 944-948.
15. Kyrou I, Chrousos GP, Tsigos C (2006) Stress, visceral obesity, and metabolic complications. Ann N Y Acad Sci 1083: 77-110.
16. Kasayama S, Saito H, Mukai M, Koga M (2005) Insulin sensitivity independently influences brachial-ankle pulse-wave velocity in non-diabetic subjects. Diabet Med 22: 1701-1706.
17. Stehouwer CD, Henry RM, Ferreira I (2008) Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 51: 527-539.
18. Wilson PW (2003) Insulin resistance syndrome and the prothrombotic state: a Framingham perspective. Endocr Pract 9 Suppl 2: 50-52.
19. Barajas L, Liu L, Powers K (1992) Anatomy of the renal innervation: intrarenal aspects and ganglia of origin. Can J Physiol Pharmacol 70: 735-749.
20. Stella A, Zanchetti A (1991) Functional role of renal afferents. Physiol Rev 71: 659-682.
21. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, et al. (2002) Sympathetic nerve activity in end-stage renal disease. Circulation 106: 1974-1979.
22. DiBona GF, Sawin LL (1982) Effect of renal nerve stimulation on NaCl and H2O transport in Henle's loop of the rat. Am J Physiol 243: F576-F580.
23. Luff SE, Hengstberger SG, McLachlan EM, Anderson WP (1992) Distribution of sympathetic neuroeffector junctions in the juxtaglomerular region of the rabbit kidney. J Auton Nerv Syst 40: 239-253.
24. Wu X, Scholey JW, Sonnenberg H, Melo LG (2000) Renal vascular morphology and haemodynamics in Dahl salt-sensitive rats on high salt-low potassium diet: neural and genetic influences. J Hypertens 18: 783-793.
25. Widmann C, Gibson S, Jarpe MB, Johnson GL (1999) Mitogen-activated protein kinase: conservation of a three-kinase module from yeast to human. Physiol Rev 79: 143-180.
26. DiBona GF (2003) Neural control of the kidney: past, present, and future. Hypertension 41: 621-624.
27. Julius S, Gudbrandsson T, Jamerson K, Andersson O (1992) The interconnection between sympathetics, microcirculation, and insulin resistance in hypertension. Blood Press: 9-19.
28. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR,et al. (2003) Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 289: 194-202.
29. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, et al. (1972) New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 30: 595-602.
30. Boudina S, Abel ED (2007) Diabetic cardiomyopathy revisited. Circulation 115: 3213-3223.
31. Di Bonito P, Moio N, Cavuto L, Covino G, Murena E, et al. (2005) Early detection of diabetic cardiomyopathy: usefulness of tissue Doppler imaging. Diabet Med 22: 1720-1725.
32. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, et al. (2000) Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 102: 1788-1794.
33. From AM, Scott CG, Chen HH (2010) The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. J Am Coll Cardiol 55: 300-305.
34. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, et al. (2010) Effect of diabetes and hypertension on left ventricular diastolic function in a high-risk population without evidence of heart disease. Eur J Heart Fail 12: 454-461.
35. Patil VC, Patil HV, Shah KB, Vasani JD, Shetty P (2011) Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function. J Cardiovasc Dis Res 2: 213-222.
36. Korosoglou G, Humpert PM, Ahrens J, Oikonomou D, Osman NF, et al. (2012)

Left ventricular diastolic function in type 2 diabetes mellitus is associated with myocardial triglyceride content but not with impaired myocardial perfusion reserve. J Magn Reson Imaging 35: 804-811.

37. Grassi G, Seravalle G, Quarti-Trevano F, Scopelliti F, Dell'Oro R, et al. (2007) Excessive sympathetic activation in heart failure with obesity and metabolic syndrome. Characteristics and mechanisms. Hypertension 49: 535-541.

38. Esler M, Jennings G, Korner P, Willett I, Dudley F, et al. (1988) Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. Hypertension 11: 3-20.

39. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, et al. (2007) Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension 50:197-203.

40. Safar ME, Protogerou AD, Blacher J (2009) Statins, central blood pressure, and blood pressure amplification. Circulation 119: 9-12.

41. Chen JY, Chou CH, Lee YL, Tsai WC, Lin CC, et al. (2010) Association of central aortic pressures indexes with development of diabetes mellitus in essential hypertension. Am J Hypertens 23: 1069-1073.

42. Van Doornum S, McColl G, Wicks IP (2004) Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. Ann Rheum Dis 63: 1571-1575.

43. Harashima K, Hayashi J, Miwa T, Tsunoda T (2009) Long-term pioglitazone therapy improves arterial stiffness in patients with type 2 diabetes mellitus. Metabolism 58: 739-745.

44. Blankestijn PJ, UMC Utrecht (2011) The Effect of Renal Denervation on Biological Variable.

45. Huang WC, Fang TC, Cheng JT (1998) Renal denervation prevents and reverses hyperinsulinemia-induced hypertension in rats. Hypertension 32: 249-254.

46. Schlaich MP, Hering D, Sobotka P, Krum H, Lambert GW, et al. (2012) Effects of renal denervation on sympathetic activation, blood pressure, and glucose metabolism in patients with resistant hypertension. Front Physiol 3:10.

47. Schlaich MP, Sobotka PA, Krum H, Whitbourn R, Walton A, et al. (2009) Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. Hypertension 54:1195-1201.

48. Baim DS (2006) Grossman's cardiac catheterization, angiography, and intervention. (7th ed) Lippincott Williams & Wilkins, Philadelphia.

49. Medtronic I (2011) The Symplicity Renal Denervation System: Procedure Overview. Medtronic, Inc,.

50. Schlaich MP, Hering D, Sobotka PA, Krum H, Esler MD (2012) Renal Denervation in Human Hypertension: Mechanisms, Current Findings, and Future Prospects. Curr Hypertens Rep 14: 247-253.

51. Granger CB, Krum H, Sella WA (2011) Catheter-Based Renal Denervation: Current Status and Future Applications. Medscape Education Cardiology: Medscape.

This article was originally published in a special issue, **Diabetic Retinopathy** handled by Editor(s). Dr. Caroline J Magri, Mater Dei Hospital, Malta