RENAL DENERVATION THERAPY

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Renal Denervation Therapy

ANCC Accredited NCPD Hours: 2.3 hrs

Target Audience: RN/APRN

Need Assessment

It is estimated that over one billion people worldwide are affected by hypertension and that over nine million annual deaths can be attributed to complications of hypertension such as myocardial infarction, stroke and renal disease. Sympathetic activation plays a major role in the pathogenesis of arterial hypertension, and renal sympathetic activation cause hypertrophy of cardiac myocytes resulting in heart failure and myocardial ischemia, insulin resistance, and insomnia. Renal denervation therapy (RDT) is an invasive procedure but, when performed by an experienced clinician, has a very low rate of complications. Renal denervation therapy therapy is usually used as a last option in patients with resistant hypertension. This is complicated by the complex pathophysiology of hypertension, lack of clinically applicable and reproducible measures of increased sympathetic activity that could be used to guide treatment decisions, and the absence of pre-procedural useful predictors of the long term BP response following it, a thorough understanding of the existing data is essential to all practitioners and clinicians.

Objectives

- Explain the role of sympathetic nervous system in Hypertension.
- Describe renal sympathetic nerve activity (RSNA) and Hypertensive Mechanisms.
- Enlist the principles of renal sympathetic denervation.
- Explain the procedure of renal denervation therapy.
- Identify the various Renal Denervation Systems currently available.
- Analyse the different categories of predictors for successful renal denervation therapy.
- Explain the determinants of Antihypertensive Response to Renal Denervation.
- Judge the concept of Renal Denervation in the treatment of Hypertension.
- Discuss Future Horizons of Renal Denervation as a medical evolution.

Goal

The goal of this article is to discover the impact of the renal sympathetic system on blood pressure regulation, the clinical rationale for renal nerve ablation in severe and drug-treatment resistant hypertension and current evidence from the more advanced renal denervation devices.

Introduction

Hypertension is a major cause of cardiovascular morbidity and mortality. Pharmacological therapies have significantly improved the outcomes of those with the condition. However, an estimated 50% of the hypertensive population remain uncontrolled with a blood pressure (BP) >140/90 mmHg, of whom a subgroup fulfill the diagnostic criteria for resistant hypertension. For those with resistant hypertension, pharmacological therapy is inadequate and alternative options are required. An overactive sympathetic nervous system (SNS) has long been shown to be an important driver of hypertension

Renal denervation is a novel procedure where the sympathetic afferent and efferent activity is reduced by various techniques and has been used successfully to treat drug-resistant hypertension improvement of various metabolic derangements. Renal denervation has the unique advantage of offering the denervation at the renal level, thus mitigating the systemic side effects. Renal denervation can be done by various techniques including radiofrequency ablation, ultrasound guided ablation and chemical ablation. Various trials evaluated the role of renal denervation in the management of resistant hypertension and have found promising results. More studies are underway to evaluate the role of renal denervation in patients presenting with resistant hypertension in different scenarios. [1, Rank 5]

> **" Renal denervation is a novel percutaneous catheter-based technique for selective renal sympathetic denervation which helps in resistant hypertension when pharmacological therapy fails to control BP. This procedure is minimally invasive, characterized by short recovery times and absence of significant systematic side effects. "**

Role of Sympathetic Nervous System in Hypertension

Renal sympathetic efferent and afferent nerves, which lie adjacent to the wall of the renal artery, are crucial for production of catecholamines contributing to hypertension. Surgical sympathectomy, targeted at removing sympathetic ganglia, to control hypertension has been reported even before the advent of newer antihypertensives. Due to its profound side effects and the introduction of pharmaceutical sympatholytic agents, surgical sympathectomy is not a preferred procedure anymore. Renal denervation is a novel technique, which involves

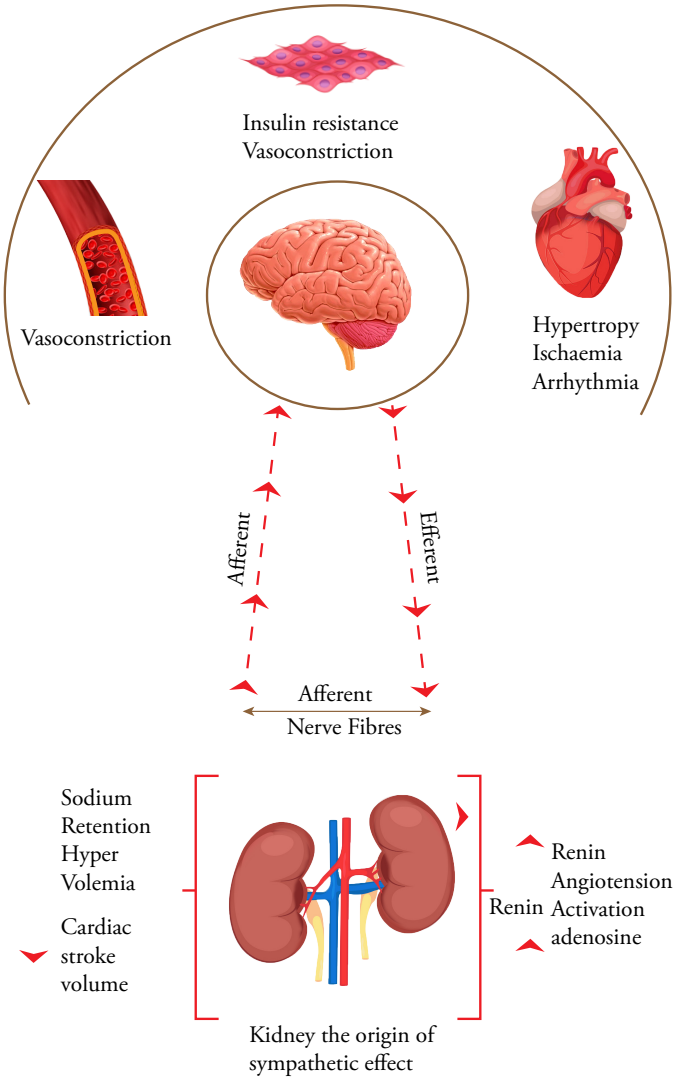

Figure 1: Kidneys and Symapthetic effects

selective ablation of renal sympathetic nerve fibres and has demonstrated promising results in controlling resistant hypertension. The renal nerves are sensitive to ablation techniques such as s radiofrequency and ultrasound. [2, Rank 4]

The Renal Sympathetic Nervous System and Hypertension

BP homeostasis is achieved by the coordinated action of several systems, and the sympathetic activity plays an important role among them. The increased sympathetic activity is correlated with all hypertensive phenotypes, and the central sympathetic drive, measured by muscle sympathetic nerve activities, is higher in the different degrees of hypertension than in normotensive patients. Additionally, norepinephrine spill-over, an index of the efferent renal sympathetic activity in hypertensive patients, augmented in parallel with an increased sympathetic outflow to the heart and the activity of the skeletal muscle sympathetic nervous system (SNS).

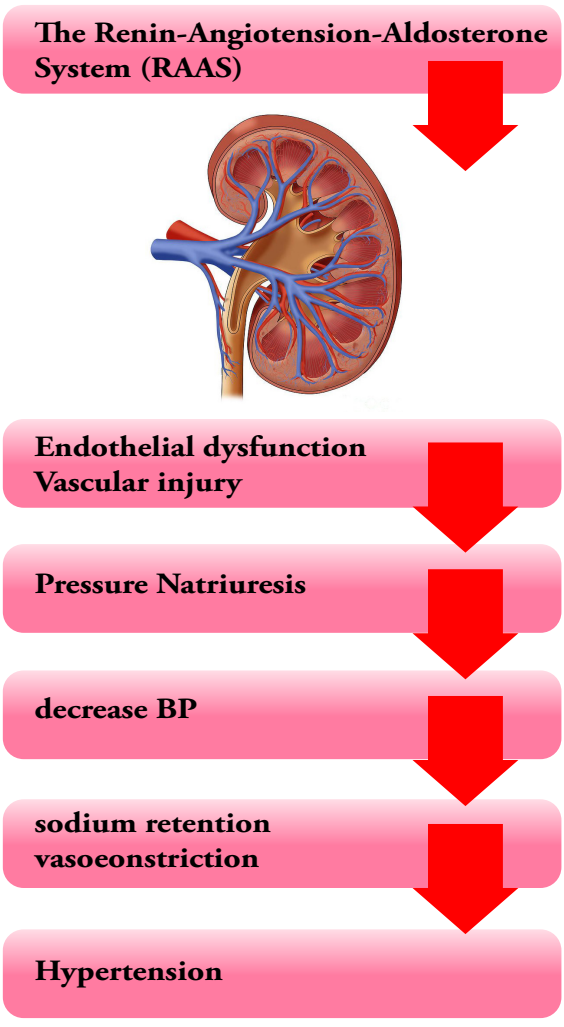

Figure 2: Renal System and Hypertension

> **"The axons of the preganglionic neurons arising from T10 to L2 interact with the renal postganglionic nerves at the level of the pre and paravertebral sympathetic ganglia. The renal postganglionic fibers run alongside the renal arteries, primarily lying around the adventitia, and finally enter into the kidney through the hilus to innervate the renal tubules, vasculature, and juxtaglomerular apparatus. By enhancing the noradrenaline production, these efferent fibers transmit stimuli from the CNS to the kidney and contribute to volume and BP homeostasis by facilitating tubular sodium reabsorption and subsequent salt and water retention, renin secretion with subsequent renin-angiotensin-aldosterone system stimulation, and renal vasoconstriction with subsequent renal blood flow reduction."**

Conversely, the kidneys transmit neural responses to the CNS via the afferent fibers, likewise located around the adventitia of the renal arteries. The cell bodies are found in the ganglia root, whereas the fiber terminations are present in all parts of the kidneys, with a higher concentration in the renal pelvis.

The fiber-ending network responds to two types of receptors:

- Mechanosensitive receptors which are linked to the hydrostatic renal pelvic, renal arterial, and venous pressure, and responds to stretch
- Chemosensitive receptors which are activated by renal ischemia, hypoxia and changes in the renal interstitial chemical concentration responds to nociception (adenosine, ischemia, acidosis, inflammation, oxidative stress, and angiotensin II)

In animal models, stimulation of the afferent system activates central nervous system centers known to be involved in cardiovascular regulation.

The returning signal is transmitted to the autonomic centre in the medulla oblongata and midbrain, where it is integrated with afferent signals originating from other districts to regulate the overall sympathetic tone, comprising that of kidneys by means of signals sent back through the efferent fibres. Therefore, this two ways communication system between the sympathetic nervous system and the kidney assumes a major role in regulating BP and in setting the overall sympathetic tone. [4, Rank 5]

Renal Sympathetic Innervation

Renal sympathetic nerves, afferent

and efferent, are embodied within the wall of the renal artery and are required for maintenance of systemic hypertension. The concept of sympathetic nerve modulation as a management tool for systemic hypertension is not new, with surgical intervention being used prior to the advent of pharmacotherapeutics.

The important role of the renal sympathetic nervous system (RSNS) in initiation and maintenance of hypertension has been demonstrated in animal experiments and experience in humans either by measuring its activity in hypertensive subjects or by monitoring BP changes after sympathetic manipulation.

The sympathetic innervation of the kidneys is composed of efferent fibers that are directed from the central nervous system (CNS) to the kidneys and afferent fibers with opposite direction, from the kidneys to the CNS. [4, Rank 4]

The kidneys are innervated by both efferent from the central nervous system and afferent to the central nervous system sympathetic nerves. The majority of nerves are unmyelinated type C fibers. The efferent nerves are approximately 25 times more abundant than afferent nerves. Stimulation of the efferent nerves in several animal models has been shown to increase renin secretion through the direct action of noradrenaline on β-adrenoreceptors on juxtaglomerular cells, promote sodium and water reabsorption at the tubular level via activation of α-adrenoreceptors, and reduce renal blood flow and glomerular filtration through vasoconstriction, all of which are important mechanisms in the pathophysiology of hypertension. In a subgroup of ten patients from the SYMPLICITY HTN-1 trial, Renal denervation therapy was able to attenuate renal efferent nerve activity with a mean 47% reduction in noradrenaline spillover.

The role of the afferent renal nerves in the genesis of hypertension is less well established. Conversely, interrupting the afferent nerves in diseased states reduces central sympathetic outflow particularly to the heart, the kidneys, and peripheral vasculature. In humans, peroneal nerve microneurography has been used to demonstrate reduced central nervous system sympathetic discharge after afferent (and efferent) renal denervation following nephrectomy in patients with end-stage renal failure and after RSD in a patient with hypertension. [6, Rank 2]

Surgical resection of thoracic, abdominal, and pelvic sympathetic nerves has been utilised in the past for the management of Stage 3 hypertension. Despite sustained blood pressure control, these methods were associated with high perioperative mortality, and long-term deleterious effects

including significant dysfunction of organs (bladder, bowel, and genitals) supplied by these nerves.

Given the efficacy of sympathetic modulation, the concept of selective disruption of sympathetic nerve supply was hypothesized. The idea was that, via percutaneous approach, a catheter can be inserted via the femoral artery and placed into the major renal artery on each side to deliver radio-frequency (RF) energy to the adventitia of the vessel, one of the layers of the arterial wall which houses the renal sympathetic and afferent nerves. The primary theoretical benefit would be sustained reduction of blood pressure, brought about by disruption of primary sympathetic output, without leading to the generalized adverse effects of broader sympathetic disruption. [3, Rank 3]

Renal sympathetic nerve activity (RSNA) and Hypertensive Mechanisms

The relationship between renal perfusion pressure and the rate of sodium excretion by the kidneys plays a major role in the regulation of body fluid volume and blood pressure. If this relationship is invariant, alterations in arterial pressure induced by changes in cardiac output and/ or peripheral resistance will lead to changes in renal sodium and water excretion that adjust extracellular fluid volume until arterial pressure returns to the initial baseline level. According to this concept, long-term changes in arterial pressure can only occur through mechanisms that alter renal pressure-natriuresis (as shown in Figure 2) Indeed, all forms of human or experimentally induced hypertension are associated with resetting of the pressure-natriuresis mechanism to a higher level of arterial pressure or to a level of renal perfusion pressure necessary for renal excretion of salt and water to precisely match intake. Since the sympathetic nervous system is commonly activated in resistant hypertension, increased renal sympathetic nervous system is a likely mechanism that impairs pressure natriuresis and thereby contributes to resistant hypertension. As indicated above, this possibility is supported by measurements showing that increased renal Nor Epinephrine spillover is prevalent in patients with resistant hypertension. A corollary of this concept is that acute responses to global inhibition of the sympathetic nervous system do not necessarily reveal the quantitative importance of neural mechanisms in mediating hypertension. While acute, global sympathoinhibition generally lowers arterial pressure within seconds to minutes, pressure reduction is not invariably sustained over the long term unless renal mechanisms are involved. In contrast, steady-state reductions in arterial pressure

in response to renal specific sympathoinhibition, such as after renal denervation, take days to manifest. [8, Rank 3]

> **" Acute arterial pressure responses to inhibition of the autonomic nervous system, such as those during ganglionic blockade, are dominated by changes in cardiac output and peripheral resistance, whereas chronic responses to neural inhibition reflect the impact of the nervous system on the more sluggish renal mechanisms for control of body fluid volume and arterial pressure. "**

Because increased RSNA shifts the pressure-natriuresis relationship to higher arterial pressure levels, the intensity of sympathetic outflow to the kidneys may be a key determinant of the antihypertensive response to renal denervation. In this regard, elucidating the mechanisms whereby increased Renal sympathetic nervous system promotes hypertension may provide greater insight into the variable responses to renal denervation in resistant hypertension. All parts of the renal vasculature are innervated with the greatest density of innervation along the afferent arterioles. Adrenergic neuroeffector junctions are also present throughout the renal tubules with the exception of the inner medulla. Renin-secreting granular cells of the juxtaglomerular apparatus also receive sympathetic innervation. This anatomic distribution of the renal nerves provides multiple mechanisms for control of sodium excretion and modulation of pressure-natriuresis. [9, Rank 4]

Through activation of different subtypes of α-adrenergic receptors on renal tubules and the renal vasculature, increased RSNA has direct effects to decrease sodium excretion by promoting tubular sodium reabsorption and by decreasing glomerular filtration rate (GFR) through constriction of the afferent arterioles (preglomerular vessels). Furthermore, activation of β-adrenergic receptors located on the juxtaglomerular cells indirectly promotes sodium retention by increasing renin secretion with subsequent generation of ANG II and concomitant aldosterone secretion from the adrenal glands. These direct and indirect effects of increased Renal sympathetic nervous system action on sodium excretion lead to a reduction in renal excretory capacity, necessitating a chronic increase in arterial pressure to achieve sodium balance. [9, Rank 3]

Overview of Renal Sympathetic Nerve Activity in Resistant Hypertension

There is now considerable evidence that the sympathetic nervous system plays a major role in the pathogenesis of primary

hypertension. In addition, recent clinical observations indicate that sympathetic activity is increased in many patients with resistant hypertension. This is not surprising as conditions associated with increased sympathetic activity such as obesity, sleep apnea, and use of blood pressure-lowering drugs such as diuretics, dihydropyridine calcium channel blockers, and vasodilators such as hydralazine are common in patients with resistant hypertension.

Measurements showing increased renal norepinephrine (NE) spillover in many, but not all, patients with primary and resistant hypertension support the hypothesis that the renal nerves provide the critical link between increased central sympathetic outflow and impairment of renal excretory function that leads to chronic hypertension. This hypothesis is further supported by studies showing that renal denervation attenuates or abolishes many forms of experimentally induced hypertension. At the same time, it is clear that renal nerve ablation does not always lower arterial pressure in patients with resistant hypertension, and the conditions for a favorable blood pressure response are largely unknown. [7, Rank 5]

Given that there are regional differences in sympathetic outflow and increased renal sympathetic nerve activity (RSNA) is expected in many patients with resistant hypertension, it is unfortunate that there are practical limitations to widespread use of the technology for assessing renal sympathetic nervous system by measuring renal Nor Epinephrine spillover. Therefore, the relationship between basal renal sympathetic nervous system and the subsequent blood pressure response to renal nerve ablation is unclear, as are the conditions that might modify a direct correlation if one were to exist.

Proponents of renal denervation for treatment of resistant hypertension often emphasize studies whereby renal denervation attenuates or abolishes hypertension in different experimental models. They also highlight clinical studies conducted many decades ago, before the advent of effective antihypertensive drugs, showing that thoracolumbar splanchnicectomy, interrupting sympathetic outflow to the kidneys, reduces the severity of hypertension in patients with severe hypertension. This perspective is often accepted without fully understanding the following relevant issues that provide a more objective viewpoint. First, the predominance of studies where renal denervation is reported to attenuate or abolish different forms of experimental hypertension was conducted in rodents. In these models, blood pressure lowering following renal denervation has not been a consistent finding. That is, in many of the same experi-

mental models of hypertension, lowering of arterial pressure by renal denervation has occurred in some but not in all studies. These inconsistencies appear to be related to differences in experimental design, such as method of blood pressure measurement, surgical technique, as well as timing of the intervention. [8, Rank 4]

The most consistent antihypertensive responses to renal denervation in rodent models of hypertension have been reported in the spontaneously hypertensive rat (SHR), a model of hypertension in which increased Renal sympathetic nervous system has been documented. However, even in the SHR, renal denervation has minimal blood pressure-lowering effects in the advanced stages of the hypertension when there is target organ damage. In dogs, there is no evidence for sympathetic activation or a contribution of the renal nerves to renal vascular hypertension (Goldblatt hypertension) or hypertension produced by chronic infusion of angiotensin II (ANG II) and aldosterone. In contrast, in the sympathetically driven model of obesity hypertension induced by feeding dogs a high-fat diet, renal denervation abolishes the hypertension before the onset of significant target organ damage These experimental studies indicate that the renal nerves do not contribute to all forms of hypertension, but that they do play a critical role in chronically increasing arterial pressure when RSNA is elevated. [8, Rank 3]

The second point often misrepresented by those promoting renal nerve ablation for treatment of resistant hypertension are the surgical sympathectomy studies conducted in hypertensive patients in the middle of the 20th century. While surgical sympathectomy in humans greatly improved mortality and survival rates, the severity of hypertension was attenuated in only about half of the 1,266 patients analyzed. These studies followed a pioneering report showing that renal denervation did not have antihypertensive effects in a patient in the early stages of primary hypertension. Based on the findings in this patient, it was concluded that "renal denervation in cases of essential hypertension is of no therapeutic value." Taken together, these observations indicate that it is misleading to base the potential merits of renal nerve ablation on only the favorable blood pressure responses to renal denervation and thoracolumbar splanchnicectomy. Clearly, there are numerous experimental and clinical observations that are inconsistent with such a superficial argument. Indeed, in recent clinical trials, renal nerve ablation has attenuated the severity of hypertension in some but not in all patients with resistant hypertension. Unfortunately, because of technical limitations in determining renal

Nor Epinephrine spillover, the only method available currently that provides a quantitative assessment of sympathetic outflow to the kidneys, clinicians are unable in routine practice to assess the relationship between the antihypertensive effects of renal denervation and baseline RSNA in patients with resistant hypertension. [8, Rank 5]

Renal Denervation in the Treatment of Hypertension

Historically, surgical lumbar interruption of the sympathetic nervous system (sympathectomy) was used for reduction of resistant hypertension before effective antihypertensive medications were available. The interest in this invasive surgical technique faded quite suddenly with the advent of the more effective antihypertensive drug therapy.

Idea that a localized endovascular approach to disrupt these nerves would theoretically result in BP reduction without the serious complications introduced by surgical sympathectomy was hinted. [5, Rank 3] In resistant hypertensive patients, renal denervation therapy was proposed in a proof-of-concept trial called the Symplicity Hypertension (HTN)-1 trial, and its encouraging results were confirmed by the Symplicity HTN-2 trial. Nowadays, a growing amount of data shows the benefits of renal sympathetic denervation in BP control, adding to previous literature evidence on the effect of surgical sympathectomy, improvement of renal function, cardiac size reduction and on the decreased incidence of headache, even if no comparison with pharmacological therapy was available at the time. [5, Rank 4]

> **" Dr. Reginald H. Smithwick was an early advocate of renal denervation (RDN), who reported splanchnicectomy in 1,266 cases with essential hypertension in 1953. Although effective when compared to conservative management available at that time, this procedure led to many adverse events, such as prolonged hospitalization, postural hypotension, syncope, impotence, difficulty in walking, and had a death rate of 10-30% and a nonresponse rate of 18-55%. "**

Blood Pressure-Lowering Effects of Renal Denervation during Antihypertensive Drug Therapy

As obesity is prevalent in patients with resistant hypertension and likely contributes to sympathoexcitation, the above interrelationships between increased Renal sympathetic nervous system and activation of the Renin Angiotensin System provide a physiological basis that may account, at

least in part, for the variable antihypertensive response to renal denervation. Because maximally tolerated doses of ACE inhibitors and ANG II blockers are part of the standard therapy for treatment of resistant hypertension, suppression of this indirect pathway for neurally induced sodium retention would be expected to diminish the antihypertensive response to renal denervation. However, pharmacological strategies to inhibit the Renin Angiotensin System may be suboptimal in some individuals with resistant hypertension as a result of incomplete blockade due to submaximal drug dosing. Counterbalancing this potential mechanism for blood pressure lowering is aldosterone breakthrough, defined as increases in plasma aldosterone concentration compared with baseline levels before blockade of the Renin Angiotensin System through mechanisms that are incompletely understood.

Because many patients with resistant hypertension have inappropriately high plasma levels of aldosterone, aldosterone excess may oppose blood pressure lowering following renal denervation by contributing to the sodium retention and intravascular volume expansion that are prevalent in these patients, despite concurrent use of diuretics. Indeed, the aldosterone antagonist spironolactone produces further reductions in arterial pressure in patients with resistant hypertension on standard antihypertensive drug therapy; however, spironolactone is not widely administered in this patient population. [10, Rank 5]

> **"In some individuals, suboptimal Renin Angiotensin System blockade may leave the indirect pathway amenable to neural modulation by renal denervation."**

Inhibition of Renal Sympathetic Nerve Activity and Renal Hemodynamics

Most renal imaging and eGFR (estimated Glomerular filtration rate) measurements conducted within the first year after renal denervation in patients with resistant hypertension indicate that the endovascular renal nerve ablation technology does not have adverse functional or structural effects that diminish kidney function. Results from the SYMPLICITY trials indicate that Glomerular filtration rate is well preserved after 6 months of renal denervation.

In contrast, in the SYMPLICITY HTN-1 registry, eGFR loss at 36 months was estimated to be 9.3 ml·min−1·1.73 m−2, a greater than twofold larger decrease in eGFR than in another recent trial in which hypertensive patients at high cardiovascular risk were treated with drug therapy. It is unclear whether the greater fall in GFR

reported in the SYMPLICITY HTN-1 registry reflects adverse effects of the technology, impaired ability of the afferent arteriole to dilate in response to a fall in arterial pressure due to persistent functional and/or structural abnormalities caused by sustained hypertension, the natural progression of resistant hypertension, or physiological responses to renal denervation. [11, Rank 4]

Obesity is common in patients with resistant hypertension, and hypertension and glomerular hyperfiltration are precursors of progressive renal injury in obesity. Therefore, the comparative renal hemodynamic responses in the dogs with obesity hypertension during global reflex suppression of sympathetic activity by chronic baroreflex activation and renal specific sympathoinhibition by surgical renal denervation may provide insight into physiological mechanisms that account for reductions in glomerular filtration rate following suppression of Renal Sympathetic Nerve Activity. In keeping with the likely physiological effects of increased Renal Sympathetic Nerve Activity in obesity, the hyperfiltration has been attributed to both a high rate of neurally mediated sodium reabsorption before the macula densa and to stimulation of renin secretion. More specifically, increased neurally mediated sodium reabsorption in the proximal tubule and loop of Henle decreases sodium delivery to the macula densa. In turn, this elicits a tubuloglomerular (TGF) signal to dilate the afferent arterioles. [10, Rank 3]

Principles of Percutaneous enal sympathetic denervation

The goal of renal sympathetic denervation is to permanently destroy a large proportion of the renal sympathetic nerves. There have been only two contemporary publications, both based on cadaveric human data that usefully describe renal nerve anatomy in man. The first studied nine renal arteries suggested that over 90% of the renal nerves are within 2 mm of the renal artery lumen (lumen–intima interface). However, these data were biased as the investigators only examined nerves up to 2.5 mm from the lumen and used inadequate histological sectioning.

The second paper studied more renal arteries included vessels that had been exposed to hypertension in vivo and employed more comprehensive histological techniques - perfusion-fixing at physiological pressures, assessment of complete periarterial nerve distribution, not just those encountered in the first 2.5 mm and application of immunohistochemistry to distinguish afferent from efferent nerves.

Based on these data, the renal sympa-

thetic nerves lie in close proximity to the renal artery (usually within the adventitia), and it is conceivable that they could be targeted by thermal energy using either radio frequency (RF) or ultrasound (US) delivered from a catheter within the renal artery lumen.

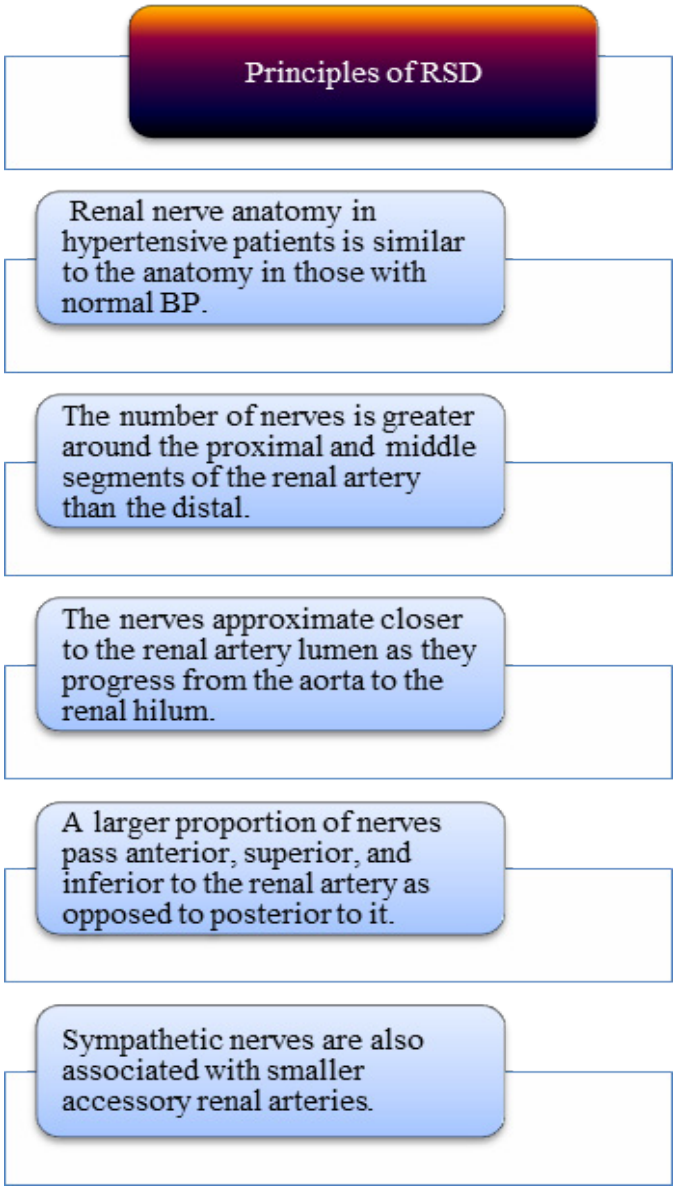

Figure 3: Principles to be followed in Renal Denervation

The original RSD trials in humans recommended that all ablations should be limited to the main vessel before any bifurcations. However, the latest histology data suggest that it might be preferential to target the distal vessel, where the renal nerves lie closer to the arterial lumen.

A strategy of performing post-bifurcation ablation was more effective at attenuating the activity of the renal sympathetic nervous system. This approach is yet to be translated to humans and, at present, should only be undertaken within the auspices of a clinical trial to ensure there are no safety concerns from possible thermal injury to the psoas muscles, small bowel, and liver. [6, Rank 3]

Renal Denervation Procedure and Technology Systems

The development of catheter-based radiofrequency ablation of the renal sympathetic nervous fiber (percutaneous transluminal radiofrequency sympathetic denervation) aims to disrupt neurogenic reflexes involved in BP control. This procedure is usually carried out using local anesthesia and conscious sedation that are required due to the intense pain experienced by patients during the ablation. Baseline aortogram is used to define anatomy, takeoff and angulation of renal arteries, vessel orientation and the presence of accessory polar arteries. Preliminary CT- or MR-based screening for suitable vascular anatomy is a useful strategy for patient

selection. Catheterization is usually introduced via the femoral artery and advanced into each renal artery under fluoroscopic control. Alternatively, a radial or brachial approach can be used.

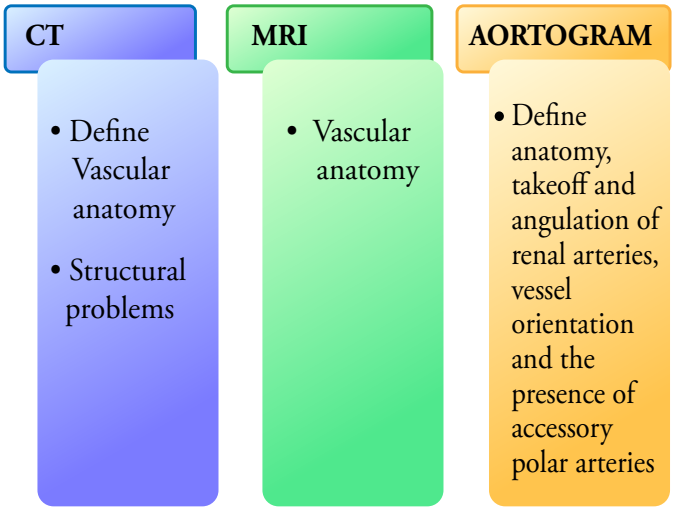

Figure 4: Assessment tests before Renal Sympathetic Denervation

After cannulation of the renal artery, a selective angiography is performed and, when needed, the device size is determined. Then, the device is gently advanced and positioned in the main branch, proximal to the bifurcation. Once the ablation device is in place, radiofrequency energy is delivered to the vessel wall according to a predetermined controlled algorithm. Impedance estimation is used to determine the correct apposition of the catheter electrodes and is monitored throughout the procedure. The application of radiofrequency energy prompts thermal heat to penetrate through the artery wall into the adventitia layer and results in denervation of the target renal sympathetic nerves. Systemic heparinization is required throughout the procedure.

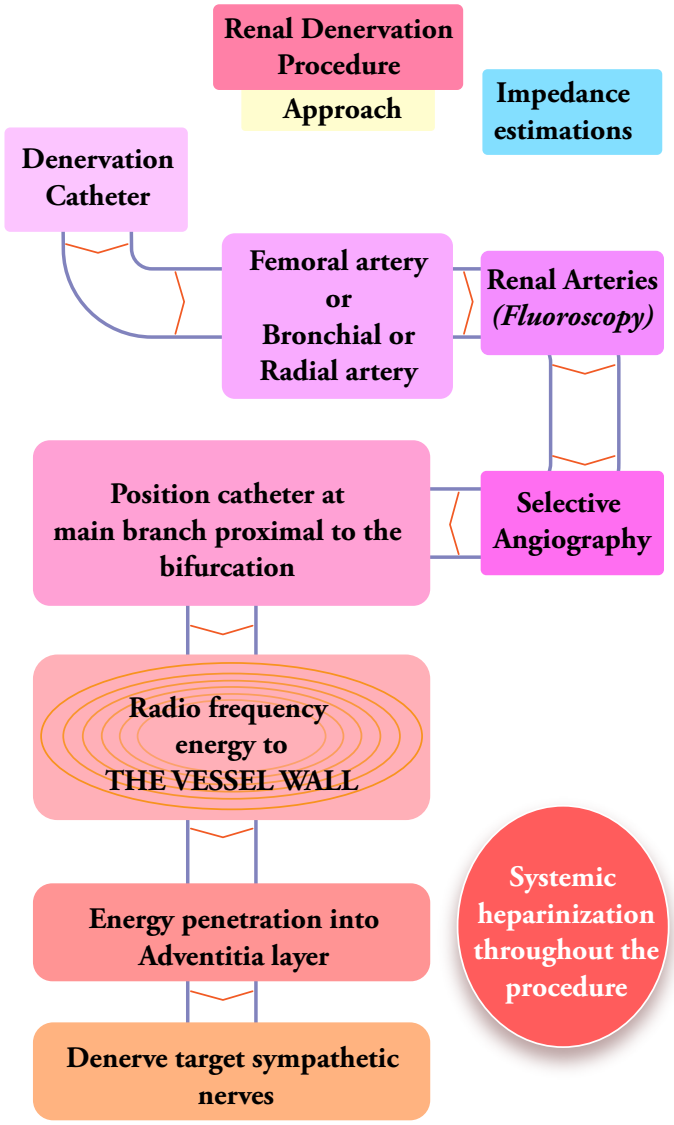

Figure 5: Procedure of Renal sympathetic denervation

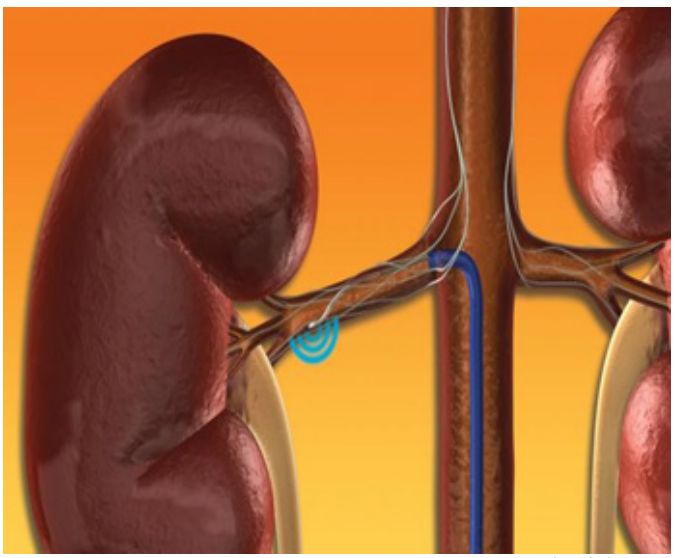

Image source: www.dicardiology.com

Figure 6: Renal Sympathetic Denervation

In general, the ablation device consists of a disposable catheter connected to a bedside console, which contains the control system, temperature and impedance monitoring and ancillary functions. [5, Rank 3]

Denervation Catheters

Once the tissue temperature reaches 50°C, irreversible cell death ensues and a lesion is created. Though the penetration of RF and US energy is likely to be just a few millimeters, the lesion depth extends further than this due to conduction of thermal energy from the initial and more superficial structures that are heated first.

Factors that influence the size of lesion created include power delivery, electrode–tissue contact, tissue impedance, and tissue temperature. During a procedure, the operator only has the ability to alter electrode–tissue contact. Power delivery is governed by proprietary and automated algorithms driven by measurement of tissue impedance and temperature taken at the electrode tip.

" During RSD (Renal Sympathetic Denervation), electrical energy at the denervation catheter tip is converted to either radio-frequency or Ultrasound Energy which penetrates through the renal artery wall and "excites" the periartery cells. This excitation creates friction between the cells generating thermal energy. "

Current Renal Denervation Systems

There are six Renal sympathetic denervation systems with the Conformite Europeenne mark, each with important design variations, such that their efficacy and safety should be considered individually rather than as a class-effect. [7, Rank 3]

The Spyral (Medtronic, Dublin, Ireland) and Vessix (Boston Scientific, Marlborough, MA, USA) system may be used in renal arteries with diameters as small as 3 mm, whereas with all the others a minimum artery diameter of 4 mm is recommended. The Iberis (Terumo Medical Corporation, Tokyo, Japan) and the Radiance (5Fr version of Paradise™ [Recor, Amsterdam, the Netherlands]) catheters can be used via the radial artery approach (all other catheters mandate operation through the femoral artery).

The maximum lesion size created by these catheters remains poorly reported. A recent review identified only four publications that adequately detailed lesion characteristics. The maximum depth of thermal injury varied from 2 to 12 mm. There needs to be more clarity about the capabilities of each system as catheters that are able to create deeper lesion might disrupt a greater

proportion of periarterial nerves and hence, be more efficacious, though this would have to be balanced against the increased risk of inadvertent damage to other abdominal structures. Recently, standards on reporting of preclinical evaluation of Renal sympathetic denervation have been published and should hopefully help improve our understanding of efficacy and risks of the various denervation systems.

It should also be noted that currently, it is not recommended to perform renal sympathetic denervation in regions of the renal artery with significant renal atheroma. Two underlying reasons for this are as follows: 1) the safety of this approach is unknown, in particular whether it may cause plaque rupture or accelerate atheroma progression; and 2) it is doubtful whether the radiofrequency energy will be able to penetrate through the atheroma to the adventitia, where the sympathetic nerves are and therefore, might expose the patient to risk without any likely benefit. [7, Rank 3]

The first device was a single electrode manually controlled device. Actually, the new devices are developed mounting the electrode on a modified balloon system or inserting different terminals on a specially designed basket-like self-expandable frame, causing a shift from an electrophysiologically based approach (i.e. ablation catheter) to a coronary interventional approach (i.e. balloon based) and making the procedure more appealing to the vascular interventionist. Additionally, the possibility to obtain multiple contact sites during a single application has the effect of shortening the procedure time and ensures a circumferential coverage of the vessel wall.

There are four devices for Renal sympathetic denervation with radiofrequency, which are currently being approved for clinical use: Medtronic Symplicity™, St. Jude Medical EnligHTN, Boston Scientific Vessix™ and Covidien OneShot™. Moreover, novel treatment modalities for RDN are under development based on ultrasound energy, cryoablation techniques, radiation, and local drug delivery. [12, Rank 5]

The Medtronic Symplicity Renal Denervation System

Figure 7: Medtronic catheter

The Medtronic Symplicity is the first system that has been used for RDN with radiofrequency. The currently used

second-generation system consists of a single unipolar electrode on the flexible tip of the catheter, with a non-over-the-wire system. It reaches a temperature up to 75°C, with an approximate energy delivery of 5-8 W in 2 min/ablation.

The catheter is directed to the vessel surface using a manipulating handle, which allows flexion and rotation to direct the catheter tip to the vessel wall. An average procedure consists of radiofrequency energy delivered for 2 min in ideally four to six different spots in a circumferential manner sequentially from distal to proximal, at least 5 mm apart, on each side. The procedure time is influenced by the operator's experience and the renal anatomy because in tortuous vessels it may be difficult to obtain an adequate vessel wall contact at all required sites. [12, Rank 3]

The St. Jude Medical EnligHTN Renal Denervation System

Figure 8: The St. Jude Medical EnligHTN Renal Denervation catheter

The St. Jude Medical EnligHTN consists of a catheter with a non-occluding nitinol basket on the tip, with four unipolar electrodes on it. There are two basket sizes of 16 mm (for 4-6 mm diameter vessels) and 18 mm (for 5-5-8-mm diameter vessels), respectively. Once the tip of the catheter is positioned, without the use of a guidewire, the nitinol basket is expanded. Once the electrodes' apposition is confirmed, it is possible to start a simultaneous, multi-electrode ablation for 90 s, using a target temperature of 75°C that needs a maximum of 6 W of switch on power, and then a lower maintenance power. After a first distal round into the renal artery, the catheter is retracted and rotated to perform another round of ablation in proximal segments or the vessel (on average, eight ablations/artery are required). [12, Rank 4]

The Boston Scientific Vessix Renal Denervation System

Figure 9: The Boston Scientific Vessix Renal Denervation Device

The Boston Scientific Vessix is a balloon-based technology consisting of a low-pressure (3 atm/304 kPa), noncompliant, over-the-wire balloon available in different sizes (4, 5, 6 and 7 mm in diameter) and a radiofrequency generator. On the balloon surface, there is a helical array of four, six or eight radiopaque bipolar electrodes, depending on the balloon size, that have independent temperature sensing and control features. Only vessel-apposed electrodes are activated by the generator when the balloon is inflated reaching a temperature of 68°C, making the procedure effective within 30 s, with a total amount of energy delivery of 1 W. [13, Rank 3]

The Covidien One Shot Renal Denervation System

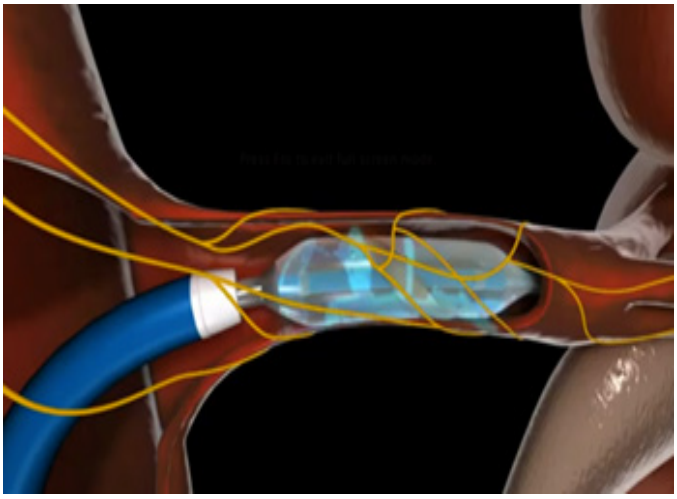

Figure 10: The Covidien One Shot Renal Denervation procedure

The Covidien OneShot is a low-pressure balloon-based system delivered over a standard 0.014″ guidewire. There are three different balloon diameter sizes (5, 6 or 7 mm) to treat vessels ranging from 4 to 7 mm of diameter, and they have a spiral silver unipolar electrode with an electrode ablation length of 20 mm and two radiopaque markers. The integrated low-pressure irrigation system allows continuous cooling of the artery during ablation, through eight tiny irrigation holes. One single 2-min ablation/artery is sufficient and delivers 25 W of radiofrequency energy and a maximum temperature of 60°C. [12, Rank 4]

Predictors for Successful Renal Denervation

Eligibility Criteria

Researchers identified three steps for the eligibility criteria for Renal Denervation. (as shown in Figure 11)

1. **Exclude patients with false resistant hypertension (pseudo resistance).**
2. **Optimizie antihypertensive treatment with at least three (or better four) tolerated drugs, including a diuretic and an antialdosterone drug.**
3. **Check the eligibility for renal denervation consists in considering anatomic contraindications due to unresolved safety issues.**

Figure 11: Eligibility checklist for Renal denervation procedure

The first step is to exclude patients with false resistant hypertension (pseudo-resistance) by using 24-hour Ambulatory Blood Pressure Monitoring and home BP monitoring, patients with secondary arterial hypertension or finally patients having high BP values due to other causes (e.g. obstructive sleep apnea, high salt intake, BP-raising drugs, or severe obesity). The second step consists in optimizing antihypertensive treatment with at least three (or better four) tolerated drugs, including a diuretic and an antialdosterone drug, when clinically possible, and then check for effective BP control using Ambulatory Blood Pressure Monitoring before giving the indication for Renal Denervation. The third and last step to check the eligibility for Renal Denervation consists in considering anatomic contraindications due to unresolved safety issues. Overall, research recommends to perform the procedure in very experienced hospital centers, such as hypertension excellence centers, and to use the devices that have demonstrated efficacy and safety in clinical studies. [15, Rank 4] Absolute contraindications arise from the Anatomic defects (as shown in Figure 12)

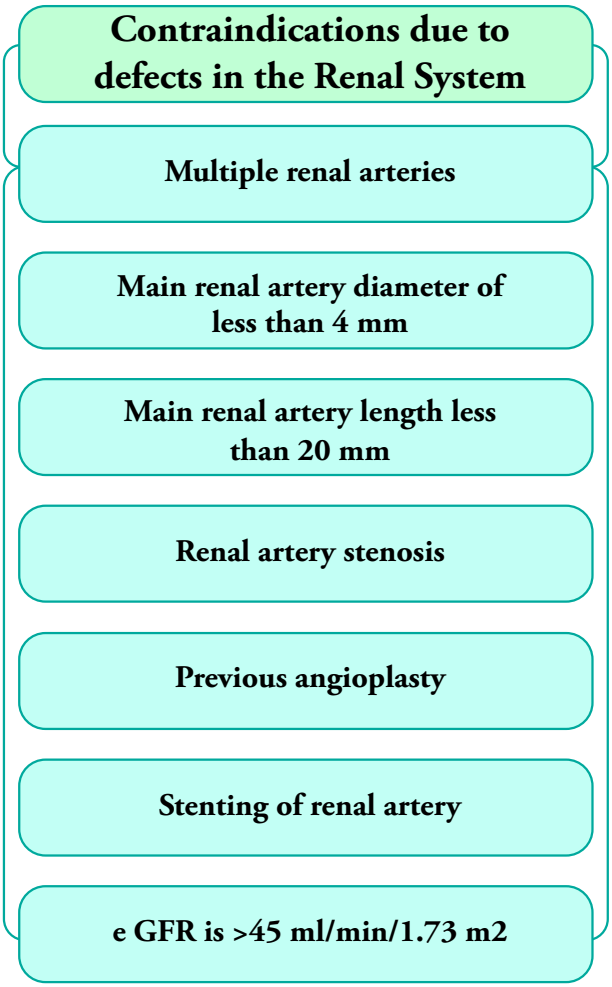

Figure 12: Contra indications for Renal Denervation Procedure

Predictors of the Outcome

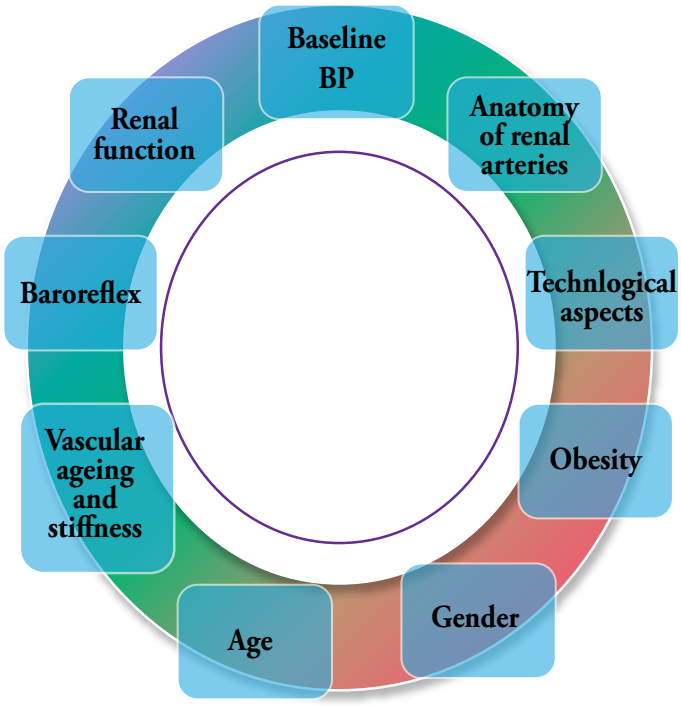

Figure 13: Predictors of Successful Renal Denervation

Baseline BP

High BP prior to renal denervation has most frequently been described as the strongest predictor of BP reduction after Renal Denervation. However, whether this is related to a higher sympathetic activity in patients with higher baseline BP or a manifestation of the regression to mean phenomenon remains controversial and is an unresolved issue to date. Thus, other predictors for treatment success in Renal Denervation are needed. [20, Rank 3]

Anatomy and technological aspects

Anatomy: The anatomy of the renal arteries seems to have considerable influence on the BP response to Renal Denervation. Importantly, the anatomy of human renal vessels shows a high variability. Accessory renal arteries or an early bifurcation occurs in approximately one of three patients. This is important, as the presence of accessory or early bifurcated vessels seems to influence outcome negatively. In principle it seems prudent to exclude these patients from renal denervation. As the sympathetic nerve fibres are closer to the lumen in the distal part of the renal vessel, ablation of the distal main artery or even the side branches are also thought to improve outcome.

Technological aspects: One of the major shortcomings of Renal Denervation is the lack of a direct feedback mechanism during intervention. Despite many promising approaches, including direct intravascular and sub cutaneous measurements of renal sympathetic activity, the challenging task of a direct in-vivo feedback for renal denervation success is still far away from clinical practice. Nevertheless, once a direct assessment method for renal sympathetic activity is established this will be a milestone in improving renal denervation success.

Another technological aspect for future trial designs is that denervation success seems to be dependent of the number of ablation points as well as the experience of the interventional physician. Therefore, Renal Denervation should only be performed by trained interventionalists and as many ablations as possible should be delivered to optimize BP outcome. [20, Rank 5]

Most clinical trials regarding Renal Denervation were carried out using radiofrequency based catheters. The role of other devices, like ultrasound-based or chemical approaches, remains uncertain, as head-to-head comparisons of different techniques are lacking. [20, Rank 4]

Obesity

Obesity seems to be associated with an elevated sympathetic activity, even in normotensive subjects. Therefore, it might be a good predictor for BP responsiveness to RDN. In contrast, according to one singu-

lar study obesity seems to be a predictor for non-responsiveness to RDN. The results of this trial are however somewhat questionable, as this constellation was neither found in any other trial nor in the even large multicenter Global Simplicity Registry. Moreover, in two smaller trials a higher body mass index was found to be a predictor for responsiveness to Renal Denervation. To date, obesity should not be considered to have any predictive value for Renal Denervation success until reevaluation in larger, adequately powered cohorts has been performed. [20, Rank 4]

Gender

So far the effect of Renal Denervation seems to be independent of gender. Nevertheless, due to the higher incidence of hypertension and therapy resistant hypertension in men, women are strongly underrepresented in any clinical trial regarding Renal Denervation. The percentage of women included in trials of renal denervation ranges between 23 and 41. Realizing a meta-analysis of prospective trials could clarify the role of gender for Renal Denervation success. [19, Rank 5]

Age

The age of the treated patients itself was not found to have a good predictive value for the success of Renal Denervation. In contrast, considerable evidence was found for vascular aging and stiffening as a predictor for renal denervation over the last years. [18, Rank 3]

Vascular aging and stiffness

Arterial stiffening is associated with a high cardiovascular mortality in hypertensive patients. It also can be regarded as a cause for essential hypertension. The presence of isolated systolic hypertension - characterized by increased aortic stiffness - is associated with a diminished response to Renal Denervation. In line with these data, researchers also found an increased aortic stiffness, assessed by invasive pulse wave velocity, to be an independent predictor for poor BP response to renal denervation. This is a promising finding, as isolated systolic hypertension and pulse wave velocity, among other markers of vascular aging and aortic stiffness, can easily be assessed non-invasively and thereby could help improving the preselection of patients available for renal denervation. [18, Rank 4]

Baroreflex

An impaired cardiac baroreflex occurs frequently in hypertensive subjects. This might be explained by sympathetic overactivity. Therefore, the presence of an impaired cardiac baroreflex as an indicator for high sympathetic overdrive could be a good predictor for renal denervation success. [18, Rank 5]

Renal function

Patients with renal diseases have often been excluded from clinical trials for safety reasons. Despite these considerations, patients with impaired renal function show an elevated sympathetic activity, and therefore might be good candidates for Renal Denervation. Consequently, an inverse relation was discovered between the estimated glomerular filtration rate and the change in BP after Renal Denervation in a hypertensive population off antihypertensive medication. However, when analysing patients on antihypertensive medication, no significant predictive value for estimated glomerular filtration rate was observed. These interesting findings warrant further investigation, as - besides enlightening the predictive role of renal function - they might partly explain why and how antihypertensive drugs interact with the effectiveness of Renal Denervation. [17, Rank 5]

Clinical Perspectives

Preclinical Data in Renal Denervation

In an extensive research study of over 300 swine, a significant ($p < 0.0001$) reduction in renal tissue norepinephrine was observed between the untreated controls ($n = 24$) and those animals receiving catheter denervation ($n = 33$) models. The safety of the procedure was verified through angiography, gross pathology, histopathology and clinical pathology at 7, 30, 60, and 180 days. Intact endothelium was found at 7 days and the arteries were well healed (no inflammatory cells were found). At 30, 60, and 180 days after treatment, the sites were considered stable and no stenosis or vessel alterations was seen in any treated artery through 180 days. [13, Rank 3]

Action and Effects

The renal nerves do have direct tubular effects to promote sodium reabsorption by stimulation of α-adrenergic receptors. However, experimental studies indicate that the indirect effects on sodium excretion, mediated via the generation of ANGIOTENSIN II, are especially important in mediating neurogenic hypertension. Therefore, the greatest antihypertensive effects of renal denervation may occur under conditions in which there is heightened renal sympathoexcitation and a Renin Angiotensin System that can respond to neural inhibition, such as in obesity, which is common in resistant hypertension. In contrast, the antihypertensive effects of neurally induced suppression of α-adrenergic receptor-mediated tubular reabsorption are minimal in the presence of aldosterone excess, which is characterized by a suppressed Renin Angiotensin System (RAS) that is invariant during alterations in renal sympathetic outflow. [15, Rank 3]

Some drugs commonly used in the

treatment of resistant hypertension such as diuretics and dihydropyridine calcium antagonists may increase renal sympathetic outflow and activate the renin angiotensin system. By extension of the above concept, renal denervation would be expected to appreciably enhance their antihypertensive effects.

Changes in activity of the renin angiotensin system play a critical role in minimizing alterations in arterial pressure during variations in salt intake. Because changes in neural activity do not appear to play an essential role in this renin response to long-term variations in salt intake, the lowering of arterial pressure following renal denervation is salt insensitive. [16, Rank 4]

Some studies indicate that resistance to therapy is associated with progressive renal damage. By decreasing preglomerular resistance and increasing glomerular pressure and glomerular filtration rate, renal denervation may predispose patients with resistant hypertension to further glomerular injury, particularly if the initial antihypertensive response is modest or absent. Careful long-term follow-up studies of greater duration than those previously conducted are needed to test whether this physiological mechanism may contribute to loss of renal function.

At present, there is only equivocal evidence from patients with resistant hypertension in support of the hypothesis that decreased input from renal afferents contributes to the antihypertensive effects of renal denervation by diminishing central sympathetic outflow. Because this concept is based on a renal injury signal from diseased kidneys, some uncertainty may occur because impaired renal function has been an exclusion criterion in most studies using renal denervation. Clarifying this concept will likely require studies including patients with reduced baseline glomerular filtration rate. [16, Rank 5]

Inflammation

Arterial hypertension is associated with chronic vascular inflammation and remodeling. In a prospective analysis of 60 patients undergoing renal denervation therapy, a significant reduction of pro-inflammatory cytokine interleukine-6 and high-sensitive C-reactive protein was achieved. This is in particular encouraging, as it might be related to beneficial long-term effects of renal denervation. It has however to be debated, if the observed changes are rather related to the BP lowering effects of renal denervation, which might attenuate the pathologic immune response, rather than to renal denervation itself. [19, Rank 5]

Safety of Renal Denervation

The overall composite complication

rate is 1.5%, which includes vascular access site complications (pseudoaneurysm, hematoma), renal artery injury (dissection, stenosis), and renal dysfunction (>50% change in renal function). The true burden of chronic complications (renal artery stenosis, deterioration in renal function), however, cannot be gauged as renal artery imaging has not been systematically performed after the procedure, the majority of studies are uncontrolled and therefore the natural progression in renal function in untreated patients with resistant hypertension cannot be directly obtained for comparison with those who underwent renal sympathetic denervation, and the majority of studies did not extend beyond 6 months of follow-up and hence, there is limited data to describe any potential harmful effects beyond this time point. Finally, since more than 90% of the published renal sympathetic denervation data have used the Symplicity catheter, the safety and efficacy data we have is attributable only to this system and should not be generalized to other products. Indeed, a small study using optical coherence tomography immediately after renal sympathetic denervation found differences in the extent of vascular damage between balloon and non-balloon-based catheter systems. These risks and uncertainties should be communicated appropriately to patients before consenting them to what currently remains a research procedure. [11, Rank 3]

Outcomes of Renal Denervation besides Antihypertensive Effects

Chronic activation of the SNS is also common in chronic kidney disease. As resistant hypertension is associated to end organ damage, the effect of RDN on kidneys was investigated. The percentage of patients for Symplicity HTN-1 registry with a follow-up of 1 and 2 years was, respectively, 41.8 and 6.5% for estimated glomerular filtration rate (eGFR). During the first year of follow-up, eGFR remained stable, while changing by −16.0 ml/min/1.73 m2 at 24 months after the procedure in patients that received spironolactone or another diuretic, which was added after the first year of follow-up. In the Symplicity HTN-2 study, no changes were reported in measured renal function with RDN, suggesting that the procedure itself and associated hemodynamic changes have no adverse effects on the kidneys even in patients with mild-to-moderately impaired renal function. [18, Rank 3]

In 15 patients with stage 3-4 chronic kidney disease, RDN caused no alterations in kidney function after a 12-month follow-up. They also performed RDN in 12 end-stage renal disease patients with uncontrolled hypertension, obtaining a significant reduction of office systolic BP at 3, 6, and 12 months. [17, Rank 4]

RDN was shown to have potential

effects on improving glucose metabolism, insulin sensitivity and sleep apnea severity but with potential limitations, including a small number of patients and interference with drug effects on insulin sensitivity, such as beta-blockers, diuretics and ACE inhibitors. It was shown that RDN decreased angiotensin receptor expression in the renal cortex of rabbits with chronic heart failure, and in diabetic hypertensive rats it reduced heart rate variability. In another study, 7 patients with chronic systolic heart failure (mean BP on referral 112/65 mm Hg) on maximal tolerated heart failure therapy were followed up for 6 months, and no procedural or postprocedural complications after RDN were found. The results suggested improvement in both symptoms and exercise capacity. Moreover, in another study with 46 patients who underwent bilateral RDN and 18 controls, the authors showed for the first time that RDN significantly reduced left ventricle mass and improved diastolic function. [18, Rank 5]

Determinants of the Antihypertensive Response to Renal Denervation

Renal afferents

The renal nerves carry not only efferent signals from the central nervous system to the kidneys but afferent information from the kidneys to the brain as well. The renal afferent limb of the sympathetic pathway emanates from both mechanoreceptors and chemoreceptors. Stimulation of pressure-sensitive mechanoreceptors by increased renal pelvic pressure inhibits sympathetic activity. In contrast, stimulation of renal chemoreceptors initiates a sympathoexcitatory reflex and is presumably activated in renal disease, seemingly in response to ischemic metabolites and/or uremic toxins. Activation of this excitatory reflex leads to an increase in central sympathetic outflow that has been postulated to contribute to the hypertension of chronic kidney disease and, more recently, resistant hypertension. [12, Rank 3]

There is a conceptual issue that is seemingly incompatible with the notion that renal afferents contribute to the sympathetic activation and increased arterial pressure of resistant hypertension. Impaired renal function has been an exclusion criterion for the renal denervation clinical trials in resistant hypertension. Therefore, because experimental data suggest that renal afferent signaling results in a sympathoexcitatory response only if the kidneys are diseased, it is questionable whether a renal injury signal is present in most resistant hypertensive patients studied to date.

Thus, while there is solid evidence that changes in efferent renal sympathetic nerve activity impact the severity of resistant hypertension, at present the data in sup-

port of a role for renal afferents in contributing to the sympathoexcitation of resistant hypertension is equivocal and, therefore, this possibility is not resolved. Thus, based on current evidence, the major antihypertensive effects of renal denervation can most likely be attributed to removal of renal sympathetic efferent fibers rather than to disruption of central input from renal sensory nerves. [12, Rank 4]

Effect of Non Epinephrine (NE)

One factor that likely influences the magnitude of the antihypertensive response to renal nerve ablation is the extent of denervation, which has not been determined in most clinical studies.

> **" Effective Renal denervation therapy may require delivery of ablative energy to the distal sections of the renal artery, near the bifurcation, rather than to just the more proximal regions of the main renal artery. "**

In the SYMPLICITY HTN-1 trial, the extent of renal denervation was determined in 10 patients by measurement of renal Nor Epinephrine spillover. In this study, renal Nor Epinephrine spillover was reduced by 47% when measured 15–30 days after renal denervation. Although a quantitative relationship between reductions in NE spillover and blood pressure lowering has not been established, based on the impressive reductions in arterial pressure reported in this study, these investigators concluded that the degree of renal denervation was sufficient to achieve therapeutic efficacy. To this point, in a study conducted in dogs with obesity hypertension, radiofrequency renal denervation lowered renal cortical Nor Epinephrine levels 42% or to about the same level as the reduction in renal Nor Epinephrine spillover in the above clinical study. In response to the 42% reduction in renal tissue levels of NE, mean arterial pressure decreased 9 mmHg. However, this decrease in arterial pressure is only 50% of the decrease that occurs with surgical renal denervation, which achieves >95% reduction in cortical Nor Epinephrine concentration along with abolishing the hypertension. Based on the heterogeneity in the reduction in renal Nor Epinephrine spillover achieved in a group of patients subjected to endovascular renal nerve ablation, with denervation being <25% in several instances, it is likely that suboptimal denervation has contributed to the inconsistent blood pressure lowering in past clinical trials. Determinations of renal histology and renal tissue levels of Nor Epinephrine in experimental studies indicate that effective therapy may require delivery of ablative energy to the distal sections of the renal artery, near

the bifurcation, rather than to just the more proximal regions of the main renal artery. As the renal nerves in the branches are closer to the renal artery lumen than they are in the more proximal regions of the renal artery, this puts the distal location closer to the ablative energy. Unfortunately, although denervation is most complete when it includes the initial branches of the renal artery, this may be technically challenging to achieve and may increase the risk of damaging the arteries. [12, Rank 3]

Other than procedural issues resulting in incomplete denervation, long-term blood pressure lowering after renal nerve ablation may also be limited by renal reinnervation. In a recent study, the Simplicity renal ablation system was used to investigate chronological changes in the renal arteries after radiofrequency renal denervation in the swine model. A total of 49 renal arteries from 28 animals with 4 different time points (7, 30, 60, and 180 days) were examined. Semiquantitative histological assessment of the arterial medial circumferential injury was greatest at 7 days and least at 180 days. The nerve injury score was significantly greater at 7 days compared with the other time points. Focal nerve regeneration at the sites of radiofrequency ablation was observed in 17% of renal arteries at 60 days and 71% at 180 days. Studies in rats, dogs, and sheep have demonstrated anatomic and functional reinnervation of both sympathetic and sensory fibers within months after renal denervation. While experimental studies in several animal species show renal reinnervation within weeks to months after renal denervation, there is limited data regarding nerve regeneration in humans following renal nerve ablation. Therefore, the time course of functional re-innervation in patients with resistant hypertension and the temporal importance of this mechanism in diminishing the antihypertensive effects of device-based renal nerve ablation are unclear at the present time. [12, Rank 4]

Renal function and sodium excretion

A potential deterioration of renal function - either by renal artery stenosis or by changes in intrarenal hemodynamics - is an often raised concern regarding renal denervation. On the contrary, as renal blood flow and salt/water retention is influenced by sympathetic activity renal denervation might have nephroprotective effects.

Two larger non-randomized analyses found glomerular filtration rates (GFR) to be unchanged after renal denervation. Interestingly, one trial could even show a decrease in albuminuria, consistent with an improvement of hypertension-induced end-organ damage. In another study, examining the effects of renal denervation in

patients with impaired renal function, the authors were able to show that the hypertension-related deterioration of renal function could be halted with renal denervation over a follow up of three years. This suggests overall beneficial effects of renal denervation on renal function, especially in these patients who already suffer from hypertension-induced end-organ damage, which will clearly improve long-term mortality. [17, Rank 4]

> **" Renal denervation does neither seem to improve nor deteriorate renal blood flow in humans and can be explained by the auto-regulative capacities of the renal vessels outweighing any renal denervation -induced changes. "**

Despite the known vasoconstrictive effects of systemic sympathetic activity on the arterial vasculature and significant alterations in an animal study, renal denervation does neither seem to improve nor deteriorate renal blood flow in humans. Presumably, this can be explained by the auto-regulative capacities of the renal vessels outweighing any renal denervation -induced changes.

The putative effect of renal denervation on renal sodium excretion is a promising therapeutic goal. The only human trial investigating this hard-to-assess endpoint however showed mixed results, as patients with stronger BP response after renal denervation showed a diminished effect on sodium excretion compared to those with less BP changes. To some extent this might be explained by a compensatory dietary sodium intake which was not assessed in the study. Therefore, this interesting aspect of renal denervation needs to be investigated thoroughly by additional rigorous assessment of dietary sodium intake. [17, Rank 5]

Systemic sympathetic activity

Direct measurement of the systemic sympathetic activity is difficult to perform and is therefore underrepresented in clinical trials of renal denervation. Indirect assessment, however, is feasible with different techniques (as shown in Figure 14)

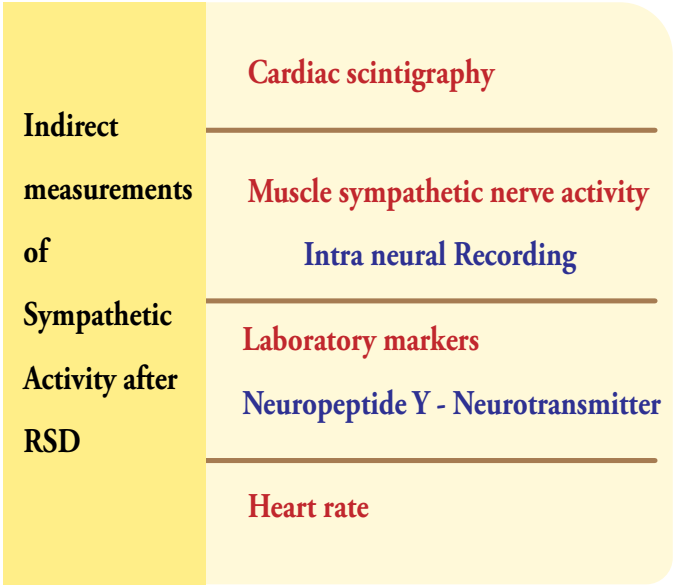

Figure 14: Indirect Assessment of Sympathetic Activity

Cardiac Scintigraphy:

> **"Myocardial perfusion scan or myocardial perfusion scintigraphy is a non-invasive nuclear medicine imaging test which uses a small amount of a radioactive tracer to investigate the blood supply to the heart."**

Two small trials (including only 23 and 11 patients) examined alterations in the cardiac sympathetic nervous system activity after renal denervation using scintigraphy. Their results were conflicting, as in one trial with only a non-significant BP drop in ambulatory BP-measurements in the renal denervation patients, no significant alterations in cardiac sympathetic activity were found. The other trial found a remarkable impact of renal denervation on ambulatory measured BP and also found a strong reduction in cardiac sympathetic activity. Since the results are inconclusive at present, further evaluation in larger, adequately powered cohorts is necessary. [18, Rank 3]

Heart rate variability

Another way to measure systemic sympathetic activity is assessing heart rate variability (HRV). In a small case series, researchers were able to show renal denervation achieved a significant reduction in patient's HRV and arrhythmia burden, suggesting a reduced systemic sympathetic activity in the treated patients. [18, Rank 2]

Muscle sympathetic nerve activity

Muscle sympathetic nerve activity is known to be elevated in hypertensive subjects, indicating a direct link to systemic sympathetic activity. Hence, direct intra-neural recordings could be considered as a good marker for treatment success after renal denervation. So far this hypothesis has been investigated in two smaller case series which failed to show any alterations through renal denervation. In contrast, a prospective controlled trial in 35 patients found significant alterations in single- and multi-unit muscle sympathetic nerve activity. Despite the latter results, overall the role of muscle sympathetic activity as an outcome marker in renal denervation trials is not fully determined and warrants further research. [18, Rank 2]

Laboratory markers:

Studies have investigated the role of Neuropeptide Y, a neurotransmitter that is co-released with norepinephrine and up-regulated during sympathetic activity. Researchers were able to show a significant drop of Neuropeptide Y after renal denervation which can be interpreted as an expression of a reduced systemic sympathetic activity.

Successful renal denervation also leads to a transient downregulation of serum brain-derived neurotrophic factor immediately after denervation. Since brain-derived neurotrophic factor is a neuronal growth factor, this adds further evidence for true downregulation of the sympathetic nervous system on a neuronal base through renal denervation . [18, Rank 5]

Overall, despite the lack of data for a direct assessment of systemic sympathetic activity in renal denervation -trials, indirect markers strongly indicate that renal denervation results in significant changes of systemic sympathetic activity. [18, Rank 4]

Future Horizons of Renal Denervation

Safety and effectiveness of BP lowering have been established in catheter-based Renal Denervation. The effect of Renal Denervation therapy on clinical outcomes, especially on cardiovascular mortality, has not been proven until today. The importance of destruction of renal nerves, beyond its antihypertensive effect, needs to be further elucidated in patients with substantial cardiovascular risk.

Renal re-innervation is only described in rats after Renal Denervation and after kidney transplantation. Whether the use of the prevalent Renal Denervation technique can permanently interrupt renal sympathetic nerve activity in humans is still to be proven, further follow-up is required beyond this time point to ascertain the longevity of the BP-lowering effect over a longer time period as well as implications regarding the need for repeat procedure.

In the HTN-1 trial, 13% of the Renal Denervation patients had little BP reduction. Among the baseline parameters, only elevated BP and use of central sympatholytic were predictors in the 24-months results. A key issue in the clinical application of the procedure is how to predict which patients may be good responder and achieve BP reduction. [13, Rank 4]

Further studies are also needed to elucidate how this procedure lowers BP and to define its clinical role in the management of hypertension and associated disorders in which the renal sympathetic outflow is activated. Hypertension may indicate the start of Renal Denervation, which could be of therapeutic value in conditions associated with sodium retention or systemic sympathetic hyperactivity.

With the increasing use of Renal Denervation, complications such as renal artery stenosis might occur more often. Safety issues will still be a subject for further investigation in a broader registration database for long-time follow-up. Further limi-

tations of Renal Denervation also include its higher costs compared to medical treatment. Additional evaluation of its therapeutic economics is needed. [14, Rank 5]

Potential Limitations of Renal Denervation

While studies have shown beneficial effects of the procedure, there are no longterm controlled data on the efficacy or sustainability of the procedure. There is also limited data on the impact of renal denervation on out-of-office blood pressure. Data from the Symplicity HTN-2 trial shows that renal denervation might not reduce ambulatory blood pressure nearly as effectively as the doctor's office blood pressure. This highlights the importance of appropriate screening of patients for white-coat resistant hypertension. Renal denervation reduces office BP and improves relevant aspects of ambulatory blood pressure monitoring in patients with true-treatment resistant hypertension while it only affects office BP in pseudo-resistant hypertension. [19, Rank 3]

Percutaneous and Minimally Invasive Approaches

A number of newer approaches have been developed to achieve specifically renal sympathetic denervation, but to avoid the complications of the earlier surgical approaches, as outlined above. Most of these approaches focus on the sympathetic nerve plexus that surrounds the main trunk of each renal artery. These nerves reside within the adventitia of the main artery or immediately adjacent. These novel approaches include various approaches to radiofrequency (RF) energy application, use of ultrasound waves, direct injection of neurotoxins such as guanethidine and even extracorporeal approaches that are completely non-invasive. [16, Rank 3]

Renal denervation in Chronic kidney disease

> **" Clonidine acting as a sympatholytic significantly decreases norepinephrine secretion and mean blood pressure in patients with chronic kidney disease. "**

Renal denervation has been studied in chronic kidney disease (CKD) - another subset of patients known to have resistant hypertension. Although the decreased clearance of catecholamines was thought to be a factor, the theory was not proven by enhanced clearance upon postural changes. Various mechanisms including increased catecholamine sensitivity, renal ischemia and decreased oxygen supply have been proposed as the reason for refractory hypertension in

chronic kidney disease patients. Nevertheless, sympathetic hyperactivity is prevalent in chronic kidney disease and its role in organ damage is well substantiated. [20, Rank 4]

Cost-Effectiveness

Patients are admitted to the hospital and observed overnight after the procedure. All the studies published so far have demonstrated blood pressure lowering affects few days to months after the procedure, there have not been reports of a precipitous immediate reduction in blood pressure after the procedure. Hence the reason for an overnight stay is difficult to justify for a procedure that is similar to most catheter based procedures performed through a femoral arteriotomy. Over 60 million populations in United States are estimated to have hypertension. Cost and appropriate patient selection would be a major determinant next to patient outcomes in implementing denervation program for hypertensive patients in the United States. Practices with certified hypertension specialists and a suitable arrangement for performing these procedures as an outpatient would be ideal for appropriate patient selection and reducing cost. [18, Rank 3]

Conclusion

Based on the results of the initial and small clinical experience, catheter-based renal denervation therapy has great promise for the treatment of refractory hypertension. Safety and efficacy findings seem to suggest that renal sympathetic denervation could be of therapeutic benefit in this patient population. Despite the fast pace of development in renal denervation therapies, significant gaps in knowledge still exist, especially with regards to possible nerve or vessel injury and long-term consequences. Further larger studies and solid randomized clinical trials are required to assess duration of BP control, quality of life, hard cardiovascular outcome, long-term safety and cost-effectiveness analysis. [15, Rank 5]

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Image Glossary

1. Figure 7: https://www.google.com/search?q=The+Medtronic+Symplicity+Renal+Denervation+System&sxsrf=ALeKk00TIdbDsYnnREQcO1IYOtXJWwT2jA:1602475261345&source=lnms&tbm=isch&sa=X&ved=2ahUKEwiGu9rFla7sAhUJyzgGHbmADCYQ_AUoAnoECAwQBA&cshid=1602475446560470&biw=1517&bih=772#imgrc=Sh_d2BXAQh_BGM

2. Figure 8: https://www.google.com/search?q=The+St.+Jude+Medical+EnligHTN+Renal+Denervation+System&sxsrf=ALeKk03Pxz0mzGFyk9o-JSnyGuMGWpi2Uw:1602475546912&source=lnms&tbm=isch&sa=X&ved=2ahUKEwiqlvDNlq7sAhVx4zgGHSglDVQQ_AUoAnoECAsQBA&biw=1517&bih=772#imgrc=f3Dq_iGkxEFxaM

3. Figure 9: https://www.google.com/search?q=The+Boston+Scientific+Vessix-+Renal+Denervation+catheter&tbm=isch&ved=2ahUKEwjV2cX8lq7sAhULwnMBHR_qA_MQ2-cCegQIABAA&oq=The+Boston+Scientific+Vessix+Renal+Denervation+catheter&gs_lcp=CgNpbWcQAzoECCMQJ1Cd1gFYneEBYIjnAWgAcAB4AIABiwKIAYkLkgEFMC44LjGYAQCgAQGqAQtnd3Mtd2l6LWltZ8ABAQ&sclient=img&ei=fNaDX9WrL4uEz7sPn9SPmA8&bih=772&biw=1517#imgrc=JkIK1hjU3HrpOM&imgdii=DkOFLldLNm_rSM

4. Figure 10: https://www.google.com/search?q=The+Covidien+One-Shot+Renal+Denervation+System&sxsrf=ALeKk02jYby_puehvBEBnZY2vVMaLAfP1g:1602475798378&source=lnms&tbm=isch&sa=X&ved=2ahUKEwiKreTFl67sAhUOyzgGHZtOBiwQ_AUoAXoECAsQAw&biw=1517&bih=772#imgrc=ZXvpDxcfcDzqVM