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Selective vs. Global Renal Denervation: a Case for Less Is More

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Abstract

Purpose of Review Review the renal nerve anatomy and physiology basics and explore the concept of global vs. selective renal denervation (RDN) to uncover some of the fundamental limitations of non-targeted renal nerve ablation and the potential superiority of selective RDN.

Recent Findings Recent trials testing the efficacy of RDN showed mixed results. Initial investigations targeted global RDN as a therapeutic goal. The repeat observation of heterogeneous response to RDN including non-responders with lack of a BP reduction, or even more unsettling, BP elevations after RDN has raised concern for the detrimental effects of unselective global RDN. Subsequent studies have suggested the presence of a heterogeneous fiber population and the potential utility of renal nerve stimulation to identify sympatho-stimulatory fibers or "hot spots."

Summary The recognition that RDN can produce heterogeneous afferent sympathetic effects both change therapeutic goals and revitalize the potential of therapeutic RDN to provide significant clinical benefits. Renal nerve stimulation has emerged as potential tool to identify sympatho-stimulatory fibers, avoid sympatho-inhibitory fibers, and thus guide selective RDN.

Keywords Hypertension · Renal nerves · Nerve stimulation · Renal denervation · Hot spots

Introduction

Renal denervation (RDN) is widely considered a promising option in hypertension (HTN) treatment since the late 2000s. Early animal work, followed by positive small to mid-scale clinical trials, supported the idea of the novel interventional treatment for HTN [1, 2]. However, the clinical and scientific community was taken aback by two sham-controlled clinical trials [3, 4] which did not reach their primary endpoint, not having significantly better blood pressure (BP) lowering in the active than the sham-arm. The most recent sham-controlled trial revealed significant heterogeneity of clinical response to unselected RDN (SPYRAL OFF-MED trial) [5]. These findings have propelled the scientific community and medical industry to re-examine initial assumptions in the physiological concept and to appreciate subtle implications of renal nerve physiology, renal nerve, and renal vascular anatomy, as well as weaknesses in clinical trial and device design. While initial investigations targeted the difficulty of obtaining adequate RDN from endovascular and external energy treatments, more recently, the assumption that global RDN is a desirable therapeutic goal has been challenged. The recognition that RDN

Several investigators have tested the feasibility of renal nerve stimulation as a diagnostic tool and a potential pathway to guide RDN therapy.

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can produce heterogeneous afferent sympathetic effects both change therapeutic goals and revitalize the potential of therapeutic RDN to provide significant clinical benefits. In this review, we will go back to the basics and explore the concept of global vs. selective RDN to uncover some of the fundamental limitations of non-targeted renal nerve ablation and the potential superiority of selective RDN.

Anatomy and Physiology of Renal Nerves

A series of macroscopic studies have examined the innervation of the kidneys. The autonomic fibers that are intended for the renal artery and kidney form the so-called renal plexus, which surrounds the artery in a net-like fashion [6, 7]. The nerves feeding the renal plexus are diverse in origin and include direct and indirect fibers from the thoracic splanchnic nerves, lumbar splanchnic nerves, aortic plexus, and the posterior vagal trunk. The combination of these fibers strongly suggests the presence of afferent communication with the central nervous system in parallel with strong sympathetic and possible parasympathetic innervation [7–9, 10••]. The various nerves typically converge in one of the three main plexi anteriors to the aorta, which include the celiac plexus, intermesenteric plexus, and lumbar sympathetic nerves, before sending off fibers to innervate the renovascular structures (Fig. 1).

The efferent fibers are co-located with the afferent fibers in the renal adventitia [12], providing the anatomic feasibility for percutaneous ablation technology (Fig. 2) [13]. All nerves are closer to the artery in the more distal segments, and parasympathetic fibers are closer to the lumen than sympathetic and afferent fibers [10••, 14••]. There is a predominance of efferent sympathetic nerve fibers. While there is a drop in density of afferent nerves from the proximal to distal renal artery [10••, 14••], the proportion of afferent nerve fibers remains constant across the length of the artery [14••] (Fig. 3).

The kidneys play a key role in fluid volume, electrolyte composition, and vascular tone, which are complex integrated processes regulated by the autonomic nervous system [15]. DiBona and Kopp suggested that the kidneys communicate with the central nervous system via three types of nerves: (1) efferent sympathetic nerve fibers, (2) efferent parasympathetic nerve fibers, and (3) afferent nerves. As an overview, efferent and afferent nerves operate in a reflex loop where afferent signals from the kidney to the central nervous system adjust the efferent sympathetic nerve output back to the kidney, and systematically. The sympathetic nervous system (SNS) receives signals reflecting alterations in renal filling pressure and chemistry and then processes information in the central nervous system where efferent signals regulate renal impact on vascular tone and volume homeostasis. Afferent nerves from the kidney parenchyma and vasculature transmit information to the ipsilateral dorsal root ganglia and then the posterior gray column. Next, the brain stem and mid-brain integrate afferent input from a number of end-organ sensors and baroreceptors [15] (Fig. 4). Efferent pre-ganglionic

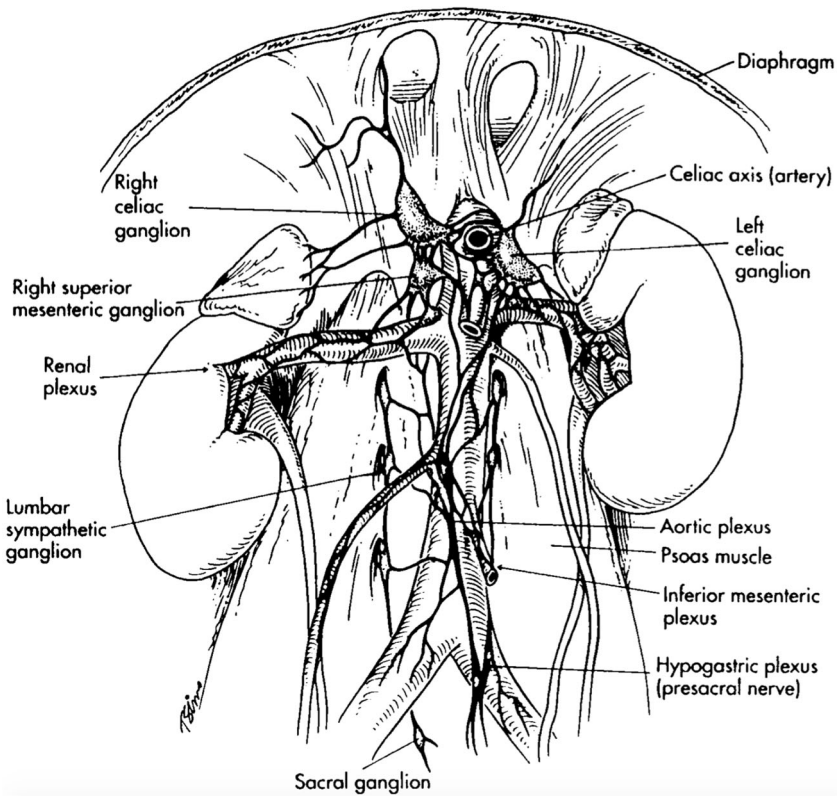

Fig. 1 Renal innervation. Reproduced with permission from Rauck RL: Sympathetic nerve blocks, in Raj PP (ed): Practical Management of Pain (ed 2). St. Louis, Mosby, 1992) [11]

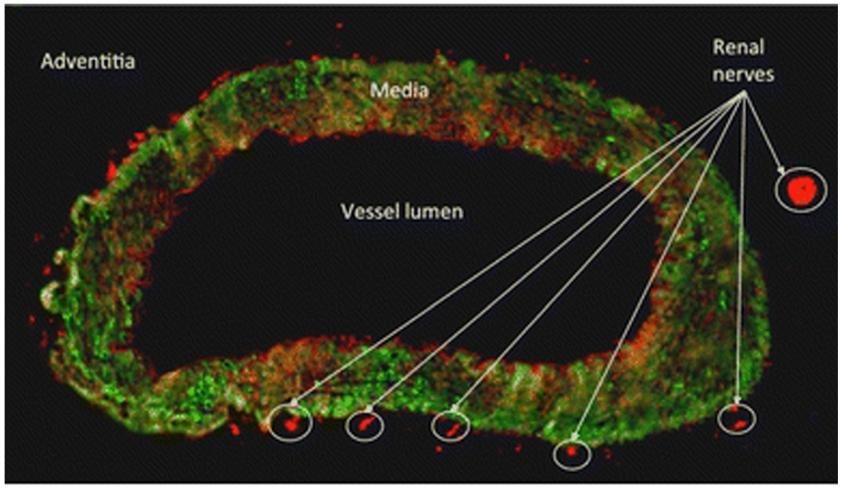

Fig. 2 Cross-sectional histology revealing the adventitial location of renal nerves. Reproduced with permission from Sobotka PA et al. Clin Res Cardiol 2011; 100 [12]:1049–57 [13]

sympathetic fibers originate from the pre-ganglionic neurons in the intermediolateral cell column and travel as splanchnic nerves to the pre-vertebral ganglia (e.g., celiac and mesenteric) to connect to post-ganglionic neurons and innervate the kidneys bilaterally [15]. However, there is likely also an intrinsic renal nervous system that reflexively auto-regulates the renal function without central nervous system input [16], the so-called reno-reflex mechanism.

Renal afferent nerves represent a diverse population of fibers, as they include myelinated and non-myelinated fibers [18, 19]. Two principal physiological types of afferent fibers provide input to the central nervous system: mechanosensitive and chemosensitive receptors. Mechanosensitive receptors communicate renal hydrostatic information from the renal arteries, veins and pelvis. Renal ionic composition, osmotic pressure, ischemia, adenosine, and chemicals (i.e. bradykinin) trigger renal chemoreceptors [15, 20]. Functionally, renal afferent fibers are categorized into three types: (1) pressor, (2) depressor, and (3) reno-renal [12, 21, 22]. The differential effect of renal afferent fibers on the global SNS results in either an elevation of the sympathetic tone (sympathostimulant) or a reduction of the sympathetic tone (sympathoinhibition), as shown across a number of animal species [22–25]. More recent pre-clinical and clinical evidence supports a more-complex-than initially expected composition and significant physiological effect of renal afferent nerves, suggesting that the intrinsic complexity of the nerve effects may play a role in the heterogeneity of observed clinical trial

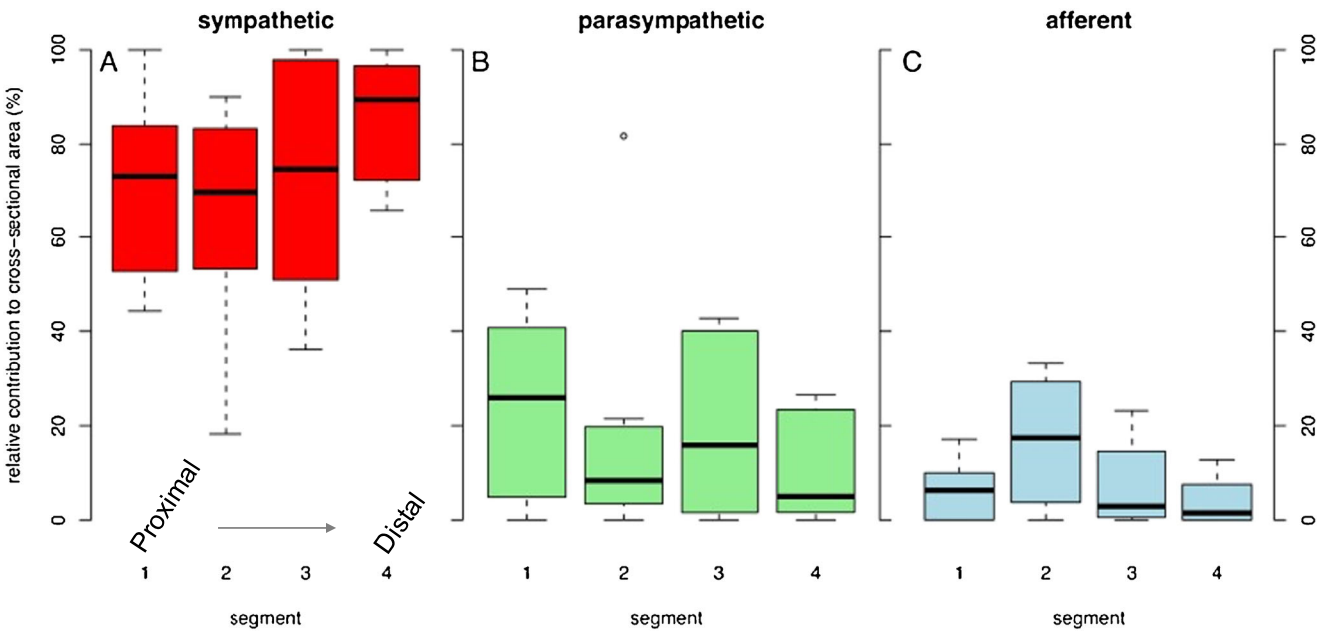

Fig. 3 Relative contributions of the nerve subtypes as a percentage of the total nerve cross-sectional area per segment. The boxes show the median value with interquartile range; the whiskers show the extreme value that is not further away from the quartiles than 1.5 times the interquartile range. The segments are ordered from proximal to distal. Modified from van Amsterdam et al. Ann. Anat. 2016 [10••]

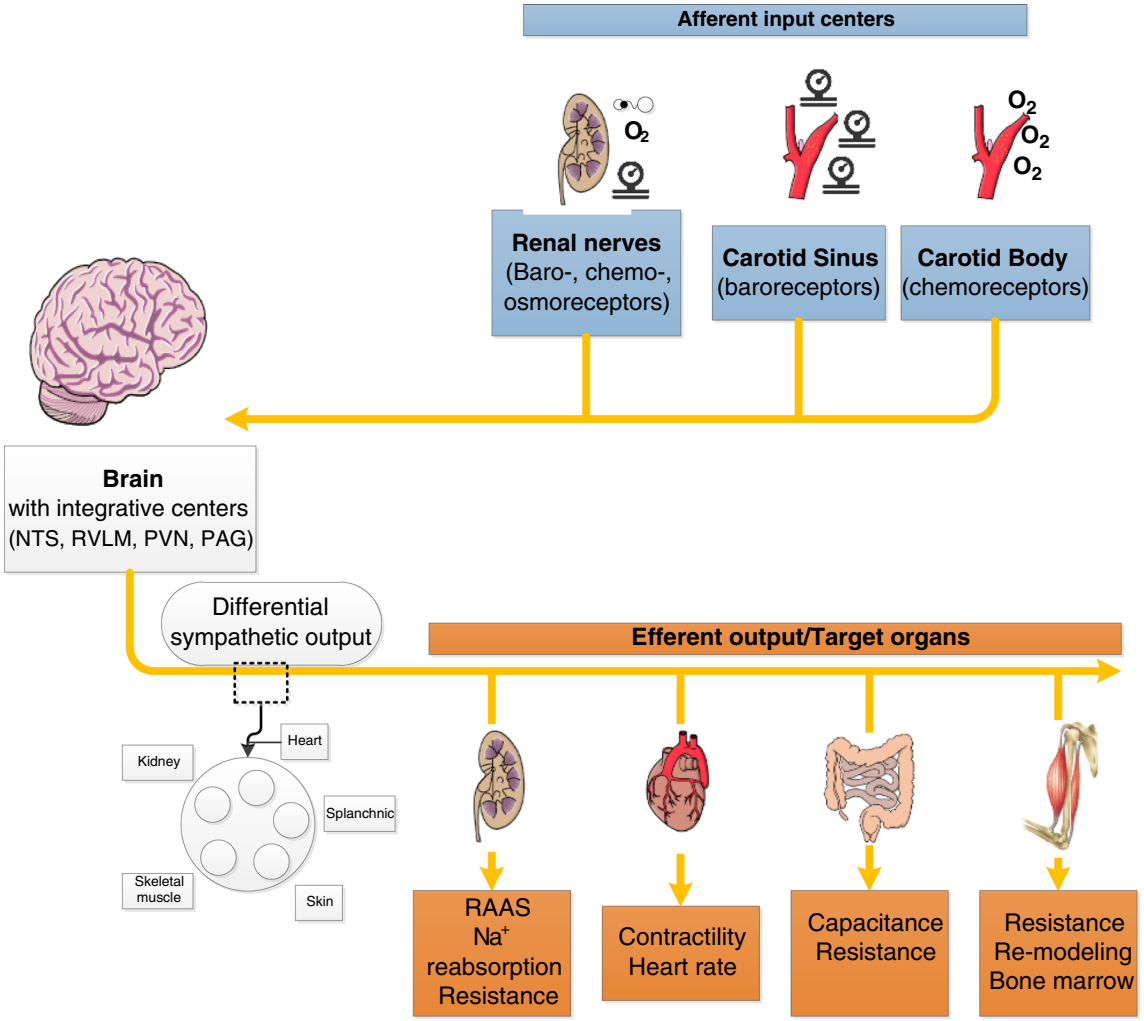

Fig. 4 Integration of afferent input and differential efferent sympathetic nerve output. Adapted from Heuser, Schlaich, Sievert. Renal Denervation: A New Approach to Treatment of Resistant Hypertension [17]

results. Endovascular electrical stimulation of renal arteries was shown to result in a varying response including an elevation in BP [26•, 27–31, 32•, 33], no effect [34], and in some cases a decrease in BP as described further below (Jie Wang SyMap 2017) [35••]. Response to afferent renal stimulation appears to depend on the site of stimulation, which may suggest that functional fibers have a characteristic anatomical distribution, with predominance of sympatho-stimulatory fibers in the proximal renal artery [29] while sympatho-inhibitory fibers are located further distally towards the renal hilum [21].

The efferent sympathetic arm of the reflex loop innervates renal vasculature, renal tubules, and the juxta-glomerular apparatus. Increased efferent sympathetic activity stimulates the β1 receptor of the juxta-glomerular apparatus to release renin [36, 37] while alpha-1B subtype receptor stimulation increases sodium resorption [37, 38]. Alpha-1A stimulation vasoconstricts renal arterioles, decreasing the renal blood flow [37, 39]. Graded input of low or high-frequency nerve signals from the central nervous system modifies the renal activity. Additionally, efferent sympathetic nerves may modulate renal venous capacitance and play a direct role in renal contribution to acute blood volume distribution [40].

The presence of parasympathetic fibers has been debated over the years. Though renal neurons positive for parasympathetic markers were demonstrated in animal models [41, 42], tracer studies could not identify a link between the kidney and the vagal pre-ganglionic fibers [43], suggesting an absence of parasympathetic innervation. Subsequently, dissections have shown both renal innervation from thoracic splanchnic nerves, lumbar splanchnic nerves, and the posterior vagal trunk, suggesting the presence of sympathetic and parasympathetic nerve fibers in animals and humans [7–9, 10••, 44]. In a recent work, van Amsterdam et al. performed the currently most extensive analysis of renal parasympathetic nerves in humans. While the authors confirmed the presence of parasympathetic fibers in the vicinity of the renal artery [10••], the physiologic function of parasympathetic nerves remains to be explored.

History of Renal Denervation: the Positives and Negatives

Pre-clinical Research

Pre-clinical research on the role of renal nerves in the pathophysiology of cardiovascular disease dates back to the 1920s. However, a few studies merit special mention. Early experiments demonstrated that electrical stimulation of feline and canine renal afferent nerves resulted in vasoconstriction-mediated BP elevation [45]. A section of afferent nerve fibers through dorsal rhizotomy in a rodent nephrectomy model precipitated a reduction in norepinephrine levels in the hypothalamus, alleviated renal function, and improved HTN, confirming the renal influence on BP regulation [46]. Finally, surgical RDN consistently lowered BP across several animal HTN models [47, 48] with favorable effects on natriuresis [49].

Surgical Denervation for Hypertension Control

Prior to the advent of anti-hypertensive pharmacotherapy, the initial attempts at HTN control included surgical thoracolumbar splanchnectomy [50, 51]. A large, prospective, observational study compared 1266 patients who underwent an extensive thoracolumbar surgical resection of nerves, resulting in non-selective interruption of renal innervation to 467 patients on medical therapy and found a durable BP decrease in combination with an improved 5-year survival (surgical 81% vs. medical 46%) [52]. Additional therapeutic benefit was seen for anginal pain, decrease in cardiac size, and improvement in renal function [51, 53, 54], though at the cost of substantial operative mortality (5%) [52] and the incapacitating side effects of autonomic blockade. Later studies, reporting the effects of nephrectomy in renal failure, noted improvement in resting sympathetic tone along with significant BP lowering, reinforcing the pathophysiological evidence for modulating renal sympathetic output as a treatment for HTN [55, 56]. Notably, surgical RDN in animals or humans comes as close as possible to a complete RDN. While surgical RDN is no longer used in humans (except sometimes in the setting of renal transplantation), complete surgical denervation in animals is often assisted by the addition of chemical nerve ablation, which modulates both efferent and afferent renal nerve activities [57, 58].

Global vs. Selective Renal Artery Denervation

With the discovery of the potential of sympathetic modulation for the treatment of HTN, various methodologies have been explored to perform RDN. Although only a surgical procedure very likely has the ability to provide complete global RDN, a targeted selective RDN restricted to only few functionally relevant sites in the renal artery might be of particular interest given several key factors: (1) An important target for RDN is afferent renal sympatho-stimulatory fibers, given their predominant contribution to the regulation of global sympathetic tone. These fibers have been repeatedly shown to be directly involved in BP control [13]. (2) Complete or limited global RDN inadvertently can affect sympatho-inhibitor fibers, potentially tipping the balance of autonomic fibers towards an increased sympathetic tone rather than a decrease. (3) Identification of renal sites without renal nerve activity to influence BP could reduce futile treatments and therapy-related treatment risk.

Due to a lack of techniques to screen for functional afferent renal fiber types, the initial technological development aimed to perform an untargeted and limited global RDN. Complete global RDN is unlikely to be achieved with non-surgical interventions given the high number of renal nerve spread across the renal arteries and renal pelvis. The currently most developed technology is endovascular radiofrequency (RF) ablation. Initial devices utilized unipolar or bipolar RF energy delivery attempting to achieve a sufficient depth of ablation to reach the adventitia and disrupt nerve traffic. Further, newer technologies have advanced to deliver pharmacoablative agents [59–61] or transmission of focused ultrasonic energy to achieve limited global ablation of renal nerves [62, 63].

The optimal location for endovascular ablation of renal nerves has been under debate for several years now. Despite some obvious benefits of more distal ablation given closer proximity of renal nerves of all types, several advantages of more proximal renal nerve ablation need to be taken into consideration. First, more proximal has a greater absolute number of renal nerves. To interpret this, a distinction needs to be made between "sympathetic nerves of passage" which pass to the kidneys and sympathetic nerves passing to the renal artery wall. The number of nerves falls passing distally, due to loss of the nerves innervating the artery wall. Second, as we have pointed out above, the number of sympatho-stimulatory fibers (Pressor) is higher more proximally, potentially tipping the benefit-risk ratio of proximal nerve ablation to be more beneficial. The early positive SYMPLICITY studies (SYMPLICITY HTN-1 and 2) recommended proximal nerve ablation sites using the SYMPLICITY Catheter system (Ardian LLC/Medronic, Minneapolis, MN) [1, 2]. The SYMPLICITY I and II studies were performed with several independent ablations using a unipolar radiofrequency system. The subsequent neutral SYMPLICITY HTN-3 study employed an updated catheter design and advised to start distally and rotate the catheter in helical patterns as the catheter is pulled back [64]. A recent randomized study comparing distal catheter-based RDN vs. standard (trunk of renal artery) in 51 patients found distal ablation to be more efficacious in lowering BP [65]. Similar findings were seen in a pig model [66]. However, these findings were not reproduced in a randomized study of 47 patients comparing full-length ablation vs. proximal RDN [67].

Selecting the Right Patient and Measuring Technical Success

The failure of the SYMPLICITY HTN-3 to establish a significant benefit from RDN and the only modest reduction in BP seen in DENERHTN [68] and SPYRAL OFF-MED trials [5] may represent technical failure of the approach, deficiencies in the device, or its application by the physician causing the intended global RDN or alternatively and importantly design failure to provide selective RDN of sympatho-stimulant (pressor) afferent fibers. In addition, lack of success could have been hampered by the improper selection of a patient population in which the renal nerve contribution to HTN is negligible. All of these factors suggest the importance of tools to assist in patient selection and confirmation of successful denervation. We have to distinguish two ways in which we can select patients for and confirm technical success of RDN: (1) post-procedural and (2) intra-procedural. The current standard is to evaluate procedural success after the RDN has already been performed (post-procedural). Markers of procedural success include the measurement of renal noradrenaline spillover or assessment of muscle sympathetic nerve activity (MSNA), which is reduced if there is afferent nerve ablation lowering central nervous system sympathetic outflow [1, 69, 70]. Both can be used to confirm denervation. RDN was found to reduce norepinephrine spillover up to 50% in humans [1]. Further, firing of single sympathetic fibers (measured by single MSNA) was reduced by 37% [71]. Reduction in MSNA, in particular, indicates that sympathetic activation can be decreased by RDN beyond the kidneys, signifying a combined modulation of efferent and afferent signaling. Yet, RDN has not been consistently found to result in a reduced local or global SNA as seen in studies using a broad range of techniques such as norepinephrine spillover, serum catecholamine levels [72, 73], MSNA [74], and cardiac/renal meta-iodobenzyl-guanidine (MIBG) scanning [75, 76].

Unfortunately, there are major limitations to all the measures of sympathetic tone mentioned above. The first limitation is that none of these techniques can serve to predict the responsiveness to endovascular RDN, in that they give retrospective results. While most techniques are technically challenging and available only at specialized centers, total noradrenaline spillover and MIBG scans give insight into central sympathetic inhibition and thus only indirect insight into renal afferent nerve activity. Application of these techniques in the setting of a catheterization laboratory is not feasible. More importantly, a reduction in sympathetic tone does not necessarily predict the degree of reduction of BP [77]. A potential explanation is the complexity of HTN pathophysiology and the variable role that SNA plays in it. Unsuccessful reduction in BP following RDN ranges from 10 to 50% [1, 78]. Comparably, changes in left ventricular hypertrophy following RDN were observed to be independent from BP improvement [79]. This indicates that long-term BP changes may not necessarily be the best surrogate marker of technical success in RDN.

The repeat observation of heterogeneous response to RDN including non-responders with lack of a BP reduction, or even more unsettling, BP elevations after RDN have raised concern for the detrimental effects of unselective global RDN potentially targeting renal afferent fibers that exert a sympatho-inhibitor function on the autonomic nervous system [5, 80]. Thus ideally, clinicians and researchers should have the ability to predict efficacy of a given RDN procedure pre- or intra-procedurally. According to the above framework, stimulation of selected renal nerves should raise arterial BP. Stimulation sites in the renal artery that are without acute biologic effect or fail to raise BP when stimulated are possibly unsafe to denervate/ablate and should be avoided. Thus, unselected RDN has risk of randomly damaging fibers that are either sympatho-inhibitor or neutral. A global denervation strategy is problematic in that it can damage protective fibers and lead to many futile ablation attempts [5] (Fig. 5).

Several investigators have tested the feasibility of renal nerve stimulation as a diagnostic tool and a potential pathway to guide RDN therapy. In a canine study ($n = 8$), electrical stimulation of the renal nerves in the proximal portion of renal artery increased the systemic BP within 30 s [28]. Changes in serum catecholamines and heart rate variability suggested that the increase in BP and heart rate caused by renal afferent nerve stimulation was attributed to an increase in systemic SNA. After ablation, stimulation-induced BP increase was significantly attenuated, while BP rise following contralateral renal artery stimulation was only mildly attenuated.

A second canine study ($n = 13$) confirmed these results and extended it by examining whether there is a differential response to renal nerve stimulation based on the site in the renal artery [29]. The investigators found that renal nerve stimulation immediately increased systolic BP > 10 mmHg in both proximal and middle regions of the renal artery. However, the BP did not increase with stimulation at the distal segments of renal artery. RF ablation was only performed over the proximal "responsive" sites (hot spots). As a result, targeted selective ablation not only prevented similar BP response with stimulation at the previously responsive sites but also attenuated the response to stimulation at the ipsilateral mid-renal arterial sites. In support of a successful ablation, the investigators saw a decrease in BP and plasma norepinephrine levels at 3 months in dogs with targeted denervation but no change in biomarkers in control animals. These findings appear to validate the anatomical framework for the ideal target for RDN, namely the sympatho-stimulatory afferent fibers (Pressor), which tend to be located in the proximal renal arteries [14••, 21, 29]. However, one study in healthy swine ($n = 10$) failed to reproduce the findings seen in the two above studies in canines, possibly indicating a species-specific contribution of

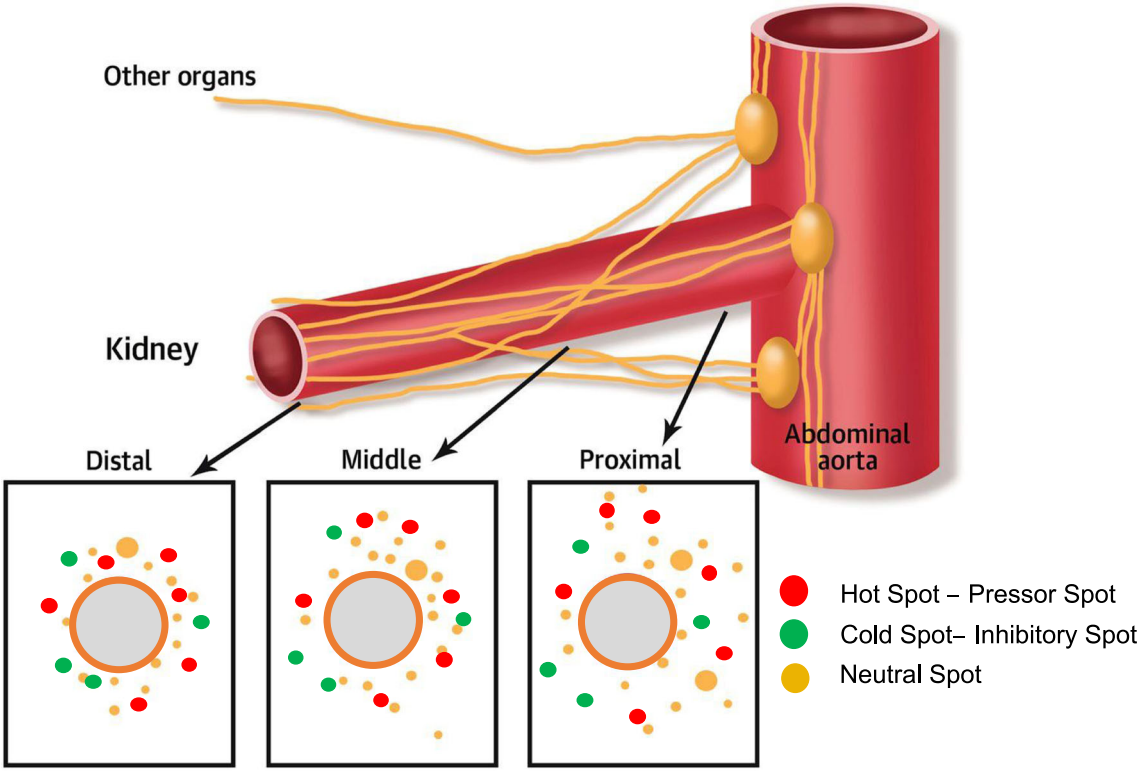

Fig. 5 Theoretical framework for selective vs global renal denervation: red lines/dots represent "hot spots"—pressor spots. These are nerves that raise the blood pressure when stimulated. They are the ideal target of renal denervation. Green line/spots represent "cold spots"—inhibitory spots, which lower the blood pressure when stimulated. The majority of nerve fibers (here in yellow) are neutral in their contribution for blood pressure physiology and do not show hemodynamic effects when stimulated. Adapted from Sakakura et al. Journal of the American College of Cardiology 2014;64:635–43 [14••]

renal nerves to the global SNA and BP [34]. An additional explanation for the observed discrepancy is the different stimulation parameters used in the swine study given other investigator reports of successful BP rise with intra-renal stimulation [81].

Preliminary animal work was followed by several human studies testing the concept of site renal nerve stimulation as a predictor of selective RDN. The published human report ($n = 8$) applied an off-the-shelf quadripolar catheter to proximal and distal sites. Interestingly, in 19.2% of stimulated sites, there was only a negligible response in BP (< 5 mmHg BP elevation) [27]. And only in 50% of patients that all stimulated sites yielded a BP elevation of > 5 mmHg. Average BP increased from 108/55 to 132/68 mmHg ($P < 0.001$) with stimulation. After RDN, systolic BP response at the site of maximum response to RNS was significantly blunted (+ 43.1 vs + 9.3 mmHg, $P = 0.002$). However, renal stimulation continued to cause systolic BP elevation in 3/8 patients > 10 mmHg, suggesting inadequate denervation at the target sites.

Pokushalov et al. performed renal nerve stimulation before RDN across the entire length of the bilateral renal arteries [26•]. RDN was intended as a supplementary treatment for patients with atrial fibrillation and hypertension. All patients ($n = 13$) showed a sudden increase in BP > 15 mmHg within seconds in response to nerve stimulation with, once again, a blunted BP response to stimulation after RDN.

De Jong et al. performed renal nerve stimulation in 4 locations on a cohort of 14 patients with resistant HTN [32•]. Stimulation resulted in a systolic BP elevation of 50 ± 27 mmHg before RDN and systolic BP increase of 13 ± 16 mmHg after RDN ($P < 0.001$). Average systolic ambulatory BP of 153 ± 11 mmHg before RDN decreased to 137 ± 10 mmHg at 3- to 6-month follow-up ($P = 0.003$). More importantly, lack of stimulation induced BP increase after RDN, indicative of successful ablation, strongly correlated to changes in ambulatory BP at 3 to 6 months (systolic BP $R = 0.77$, $P = 0.001$ and diastolic BP $R = 0.79$, $P = 0.001$). In a separate study of 21 patients, the intention was to test whether BP elevation could be induced by stimulation of non-denervated accessory renal artery sites. While renal nerve stimulation-induced systolic BP raise was blunted in the main renal arteries, stimulation of the non-denervated accessory, renal arteries did produce an unchanged BP increase after local stimulation (Δ systolic blood pressure, 27.1 ± 7.6 mmHg; $P = 0.917$). Results of this nature suggest that non-denervated sites, whether in the proximal or distal renal artery trunk or accessory renal arteries, can be the residual source of afferent renal sympatho-stimulatory input propagating persistent HTN after

Table 1 Blood pressure response to renal stimulation before renal ablation ("hot spots"—pressor spots). From Jie Wang, SyMed 2017

		SBP (mmHg) Before	SBP (mmHg) After	▵SBP (mmHg)	DBP (mmHg) Before	DBP (mmHg) After	▵DBP (mmHg)	MAP (mmHg) Before	MAP (mmHg) After	▵MAP (mmHg)
Renal nerve stimulation Before RDN	Mean	172.1	185.9	13.8	87.1	94.9	8.1	116.9	124.6	8.2
	SE	4.4	4.5	1.1	2.4	2.4	0.7	2.8	2.7	0.8
Renal nerve stimulation After RDN	Mean	169.8	170.5	0.7	89.4	89.6	1.2	115.4	116.8	0.2
	SE	4.8	4.8	1.4	2.9	2.9	0.8	3.8	3.0	0.9

RDN and account for the large response variability seen across RDN studies to date.

Interestingly, intra-renal artery stimulation is not the only approach to stimulate renal nerves as a means to elevate the BP and identify sympatho-stimulatory fibers. Madhanav et al. reported a case of transvenous renal nerve stimulation with an off-the-shelf RF catheter, indicating a close proximity of renal nerves to both the renal artery and vein [33]. So far, this observation has not been investigated as a potential treatment.

The recent introduction of dedicated combined diagnostic and ablation systems [81] could facilitate appropriate patient selection through screening for candidates whose BP is driven by renal nerve activity. This would allow the operators to target only optimal ablation sites (sympatho-stimulatory) while minimizing damage to sympatho-inhibitor sites, with documentation of technical success through the loss of systemic BP and heart rate changes following RDN. The ongoing Sympathetic Mapping/Ablation of Renal Nerves Trial (SMART Study, ClinicalTrials.gov ID: NCT02761811) aims to confirm clinical benefit of selective RDN with the use of the dedicated electromapping SyMapCath I™ catheter and SYMPIONEER S1™ Stimulator/Generator. Preliminary data from SMART Study were presented at International Conference for Innovation (ICI, Tel Aviv) in 2017 and CRT 2018 (Washington DC) [35••] and confirm some of the theoretical groundwork and preliminary data laid out above. In ten patients with resistant HTN, only 54% of sites were responsive to stimulation with BP elevation (hot spots) (Table 1). Maybe most importantly, stimulation resulted in a BP drop in 16% of sites (systolic − 16 mmHg, diastolic − 4 mmHg, and mean − 7 mmHg in average) (Table 2) and no BP response to stimulation in 29% of sites. As seen before, ablation of the hot spots prevented BP elevation with repeat stimulation intra-procedurally. Long-term outcomes in the full study cohort are still pending. Similar attempts to develop an integrated mapping and ablation system are also made by Rainbow/Pythagoras. Preliminary results were recently presented by Mahfoud, Tsioufis, and Damen at EuroPCR 2017 and confirm a heterogeneous response to renal nerve stimulation based on location of stimulation with a tendency towards higher BP elevation with higher levels of energy in more proximal renal artery locations [82••]. The continued development of appropriate tools to test the renal nerve contribution to elevated BP confirms technical success of RDN and in the end allows guidance of RDN, which appears to be in close reach.

The safety of renal stimulation should be taken into consideration. A very recent study showed increased ventricular tachycardia burden in an acute myocardial infarction canine model after renal nerve stimulation [83]. No such effects on the arrhythmia burden were seen in normal hearts. More research on the effects of temporary renal nerve stimulation is needed.

The promise of a targeted selective RDN opens up a number of possibilities which could address the limitations previously experienced with the conventional approach of unselective or global RDN. Dedicated clinical studies will need to prove the efficacy of the selective RDN approach on long-term BP reduction. Additionally, RDN holds promise in favorably identifying the pathophysiology of multiple chronic diseases such as diabetes, arrhythmias, obstructive sleep apnea, heart failure, and chronic renal insufficiency, as these disease forms are strongly associated with overactivity of the SNS. And modulation of sympathetic tone may have additional salutary effects beyond lowering BP [84–87].

Table 2 Blood pressure response to renal stimulation before renal ablation ("cold spots"—inhibitory spots). From Jie Wang, SyMed 2017

	SBP (mmHg) Before	SBP (mmHg) After	▵SBP (mmHg)	DBP (mmHg) Before	DBP (mmHg) After	▵DBP (mmHg)	MAP (mmHg) Before	MAP (mmHg) After	▵MAP (mmHg)
Mean	167.6	151.5	− 16.2	92.2	88.0	− 4.2	118.1	109.7	− 6.8
SE	6.7	6.4	1.7	3.7	4.1	0.9	4.6	4.5	1.5

Compliance with Ethical Standards

Conflict of Interest Dr. Fudim is supported by an American Heart Association Grant, 17MCPRP33460225 and NIH T32 grant 5T32HL007101; he consults for Coridea, AxonTherapies, and Galvani. Dr. Sobotka is an employee of ROX Medical, Inc.; is consulting for SyMap. Dr. Yin is a consultant for SyMap. Dr. J. Wang is a co-founder of SyMap Medical Ltd. Dr. Esler is supported by a Senior Principal Research Fellowship of the National Health and Medical Research Council of Australia. The other authors declare no conflict of interest relevant to this manuscript. Paul Sobotka

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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