Renal Denervation Update From the International Sympathetic Nervous System Summit: JACC State-of-the-Art Review

Marcio G. Kiuchi[1], Murray D. Esler[2], Gregory D. Fink[3], John W. Osborn [4], Christopher T. Banek[4], Michael Böhm[5], Kate M. Denton[6], Gerald F. DiBona[7], Thomas H. Everett IV[8], Guido Grassi[9], Richard E. Katholi[10], Mark M. Knuepfer[11], Ulla C. Kopp[12], David J. Lefer[13], Thomas E. Lohmeier[14], Clive N. May[15], Felix Mahfoud[5], Julian F.R. Paton[16,17], Roland E. Schmieder[18], Peter R. Pellegrino[19], Yehonatan Sharabi[20], Markus P.Schlaich[1, 2]

[1]Dobney Hypertension Centre, School of Medicine - Royal Perth Hospital Unit, University of Western Australia and [2]Departments of Cardiology and Nephrology, Royal Perth Hospital, Perth, Australia. [2]Neurovascular Hypertension & Kidney Disease Laboratory and Human Neurotransmitter Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. [3]Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan, USA. [4] Department of Integrative Biology and Physiology, University of Minnesota, Minneapolis, Minnesota, USA. [5]Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany. [6]Cardiovascular Program, Monash Biomedicine Discovery Institute and Department of Physiology, Monash University, Melbourne, Victoria, Australia. [7]Department of Internal Medicine and Molecular Physiology and Biophysics, University of Iowa, Carver College of Medicine, Iowa City, IA, USA. [8]The Krannert Institute of Cardiology and Division of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA. [9]Clinica Medica, Dipartimento di Medicina e Chirurgia, Università Milano-Bicocca, Milano, Italy. [10] Prairie Heart Institute at St. John's Hospital, Department of Cardiology, Springfield, IL, USA. [11]Department of Pharmacology and Physiology, St. Louis

University School of Medicine, St. Louis, MO 63104, USA. [12]Departments of Internal Medicine and Pharmacology, University of Iowa Carver College of Medicine, Iowa City, IA, USA. [13]Cardiovascular Center of Excellence and Department of Pharmacology, LSU Health Science Center, New Orleans, LA,USA. [14]Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA. [15]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Victoria, Australia; [16]Department of Physiology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand. [17]School of Physiology, Pharmacology & Neuroscience, Biomedical Sciences, University of Bristol, Bristol, UK. [18]Department of Nephrology and Hypertensiology, Clinical Research Center, University Erlangen-Nuremberg, Erlangen, Germany. [19]Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, NE, USA. [20]Chaim Sheba Medical Center and Tel Aviv University Sackler Faculty of Medicine, Israel.

Total word count: 3866 words

Short title: Proceedings from the SNS Summit 2018

Correspondence to:

Winthrop Professor Markus Schlaich

Dobney Chair in Clinical Research

School of Medicine - Royal Perth Hospital Unit

The University of Western Australia

Level 3, MRF Building, Rear 50 Murray St,

Perth WA 6000; Australia

Phone: +61 8 9224 0382 Fax: +61 8 9224 0374

e-mail: markus.schlaich@uwa.edu.au

Abstract

The promising results derived from the Symplicity HTN-1 and HTN-2 trials moved catheter-based renal denervation (RDN) on to centre stage as a potent adjuvant tool to lower blood pressure (BP) in resistant hypertension by targeting renal and central sympathetic activity. However, the Symplicity HTN-3 trial failed to confirm the superiority of RDN in reducing BP compared to a sham procedure. Recently, the SPYRAL HTN-OFF MED and RADIANCE-HTN SOLO trials, both in drug-naïve hypertensive patients, and the SPYRAL HTN-ON MED trial in hypertensive patients on concurrent antihypertensive therapy, demonstrated a clinically significant reduction of ambulatory blood pressure in comparison to respective sham control groups. Improved trial design, selection of relevant patient cohorts, and optimized interventional procedures have likely contributed to these positive and promising findings. However, substantial variability in the BP response to renal denervation across cohorts of patients can still be observed and it remains a challenging and important problem to identify those patients that will respond to the procedure.

The International Sympathetic Nervous System (SNS) Summit was convened to bring together experts in both experimental and clinical medicine relevant to the SNS and its modulation. Its aim was to discuss the current clinical evidence base, novel developments in our understanding of the interplay between afferent sensory and efferent sympathetic signaling, procedural aspects to further optimize treatment efficacy/monitor technical success, pre-procedural prediction of response, the potential role of nerve regrowth post denervation and define best outcome variables.

Identification of relevant trends in the field and initiation of tailored and combined research efforts, both experimentally and clinically, to address these aspects are likely to advance this important field further and will provide much-needed evidence to guide the best

clinical use of renal denervation for hypertension and other potential applications. This article attempts to consolidate the current viewpoints of some experts in the field and proposes directions where research energy could be applied in the future to improve the treatment outcome and understanding of renal denervation in human hypertension.

Renal Denervation: Current State of The Art

The initial results from the Symplicity HTN-1 (1) and HTN-2 (2) trials moved catheter-based renal denervation (RDN) as a novel approach to lower blood pressure on to centre stage in cardiovascular medicine. In these initial trials, RDN was demonstrated to be a safe and effective in lowering blood pressure (BP) in subjects with resistant hypertension via a reduction in renal and central sympathetic activity (3, 4). However, the sham-controlled Symplicity HTN-3 trial (5) failed to demonstrate superiority of RDN in reducing BP compared to a sham group at six months post-procedure. These unexpected findings have been discussed extensively and controversially in the literature. The failure of the trial was attributed to several possible confounding factors, including issues related to patient selection and medication adherence, suboptimal procedural performance, and operator experience, amongst others (6). The Symplicity HTN-3 results significantly impacted other research studies and clinical trials in the field. It was not rectified until the multicenter, randomized-controlled DENER-HTN study showed a clear signal for supremacy of RDN and a standardized stepped-care antihypertensive treatment approach over the same standardized stepped-care antihypertensive treatment alone in patients with resistant hypertension (7),. Importantly, the prevalence of non-adherence to antihypertensive drugs at six months was high (~50%) but not different in the renal denervation and control groups (8) in this study.

Non-adherence to antihypertensive medications is highly variable over time in clinical trials (9, 10). Tomaszewski and colleagues demonstrated that a significant proportion of patients in a specialist center show at least some degree of treatment non-adherence and that their BP levels correlate well with the degree of non-adherence (11). Furthermore, patients with undeclared/unrecognized non-adherence frequently undergo numerous additional (sometimes invasive and often expensive) diagnostic tests in specialist centers to identify the causes of their apparent poor response to antihypertensive medications. Moreover, patients who are non-adherent to antihypertensive treatment fail to gain the proven benefits of BP lowering therapy and remain at high risk of cardiovascular events. The SPYRAL HTN-ON MED proof-of-concept randomized trial (12) showed antihypertensive medication adherence ~60% and variation for individual patients throughout the study. It suggests that at least some patients do not perceive their physician's advice as the most suitable or ideal option for their condition, demonstrating patient preference. In non-adherent antihypertensive treatment patients, RDN would be a safe and innovative option once new and consistent evidence arose from RDN trials in drug-naïve hypertensive patients regarding BP reduction (13, 14).

More than a decade after the publication of the original proof-of-concept study and perhaps inflated expectations some important recent studies paved the way for resumption of investigative interest**,** including the DENERHTN trial (7), the SPYRAL HTN-OFF MED (13) and RADIANCE-HTN SOLO (14) trials, both in drug-naïve hypertensive patients, as well as, the SPYRAL HTN-ON MED trial (12) in hypertensive patients on concurrent antihypertensive therapy. All demonstrated a clinically significant reduction of ambulatory BP in comparison to respective sham control groups (Figure 1). Evidence is therefore now available from 3 consecutive and adequately designed, randomized, sham-controlled trials confirming the BP-lowering efficacy of catheter-based RDN approaches (15).

With pivotal trials now underway for several RDN devices, such as SPYRAL-PIVOTAL, for example, it is perhaps pertinent for the hypertension community to develop strategies on exactly how to best allocate the limited resources to ensure the availability of RDN for those individuals who are most likely to benefit. To achieve this goal, intensive research efforts are required to address the most critical unresolved issues. These issues and related recent research findings are discussed below.

New Insights into RDN-induced BP lowering mechanisms

Renal Efferent Signaling: The renal efferent nerves are mostly adrenergic. Norepinephrine release mediates vasoconstriction of the renal vessels, as well as sodium and water reabsorption at renal tubular epithelial cells, and renin discharge from the juxtaglomerular cells (16).

The mechanism(s) by which RDN attenuate(s) any form of hypertension is a subject of considerable debate. One explanation is that RDN increases renal sodium and water excretion and causes a subsequent contraction of blood volume (17) by suppressing sympathetically mediated renin secretion and/or sodium reabsorption. However, Foss and colleagues found no differences in daily or cumulative sodium and water balance between SHAM and RDN rats (18). This is consistent with previous reports that RDN decreases BP in normotensive Sprague Dawley rats independent of sodium balance or renin release (19, 20). It is important to note that RDN did not affect the salt sensitivity of arterial pressure in Sprague Dawley rats (17) or Dahl salt-sensitive (DS) rats. Combined with their findings that afferent renal nerves do not play a role in DS rat model, these data suggest that the antihypertensive effect of RDN in the DS rat is likely due to reduced activity of the renin-angiotensin system, a reduction in renal vascular resistance, or another effect of efferent renal nerve ablation. Further investigation will be needed to test these possibilities (21).

Another mechanism may involve the rostral ventrolateral (RVLM) which provides a major excitatory drive to efferent RSNA. The level of RSNA is reliant on the neuronal activity in sympathetic premotor nuclei in the brainstem and hypothalamus, including the RVLM and ventromedial (RVMM) medulla as well the paraventricular nucleus (PVN). The notable reduction in BP after the destruction of premotor neurons in the RVLM is suggestive of its importance in the maitenance of arterial pressure. (22). Inhibition of renal efferent signalling after RDN with downstream effects on the renin-angiotensin-aldosterone cascade and renal arteriolar dilatation are likley contributors to the BP lowering efficacy.

Renal Afferent signalling: Recently, Tsai and colleagues demonstrated in ambulatory canines that bilateral RDN, possibly via interrupting afferent innervation, led to substantial brain stem and bilateral stellate ganglion remodeling, at eight weeks post-procedure (23). These changes were associated with reduced ^{18}FDG- uptake in the brainstem, left stellate ganglion nerve activity and atrial tachyarrhythmia events. They propose that neural remodeling in the brain stem and stellate ganglion may partially explain the described antiarrhythmic effects of RDN (23).

Trans-synaptic degeneration is a phenomenon in the central and peripheral nervous system that may remain active both at the level of the insult and in remote brain structures for as long as one year after a trauma (24). These progressive alterations may underlie some of the long-term functional consequences after initial injury (i.e. RDN) as shown in ***Figure 2***, which summarizes the various direct and indirect connections between renal sympathetic nerves and the stellate ganglion. Meckler and colleagues showed that only 10% approximately of bilateral renal sympathetic neurons in cats originated from the thoracic chain ganglia (stellate through T13) (25). Because of the connections between these two structures, RDN may directly result in retrograde cell death of some neurons within the stellate ganglion. Furthermore, the

application of fluorescent dyes in the renal nerves results in fluorescent labeling of some sympathetic cell bodies in paravertebral and prevertebral ganglia (26-28).

Since the sympathetic preganglionic neurons that project to the stellate ganglion are dispersed in spinal sections T1-T10 (29), they have ample chances to interrelate with the preganglionic cells that link indirectly with sympathetic nerve fibers surrounding the renal arteries. However, some other pathways might contribute to trans-synaptic degeneration post-RDN(23), as the ganglion cells of renal afferent nerves situated in thoracic and lumbar spine dorsal root ganglia that link to the posterior and lateral hypothalamic nuclei, as well as, the locus ceruleus in the brain stem (30, 31). All these types of connections suggest one cause of persistent effects of RDN may be remodeling of the critical brainstem areas and the stellate ganglia, and, perhaps, a lowering of the set-point of arterial pressure governed by sympathetic networks.

Methods to assess the efficacy of RDN

Unlike coronary interventions, current renal denervation devices provide no feedback to the interventionalist regarding technical success of the procedure. As a consequence, the degree of denervation is uncontrolled (32), and inadequate renal denervation was implicated in the failure of Symplicity HTN-3 to show a BP benefit (5, 6). Despite more recent positive clinical trials (12-14), intra-procedural validation of adequate renal sympathetic and afferent nerve ablation remains a fundamental challenge in the field.

Validation of successful renal denervation in preclinical studies has been achieved in four ways: histopathology, direct neural stimulation, reflex elicitation, and passive monitoring. While histopathology is considered the gold standard for validation of renal denervation in preclinical studies, this approach is unsuitable in patients. The other three modalities are the

subject of exciting new technologies which are being translated to the clinic to provide intra-procedural validation of renal denervation (***Figure 3*****).**

Direct Neural Stimulation of Afferent Renal Nerves: Available RDN trials have shown that the response to the procedure is variable with a proportion of non-responders, i.e., the absence of a significant BP reduction, or even BP elevations post-RDN. This could be due merely to differing degrees of RDN (i.e. "completeness" of nerve damage, as mentioned above). Another possibility is that activity in some renal nerves promotes increases in BP while activity in others (especially sympatho-inhibitory afferents) leads to a fall in SNA and BP. Ablation of primarily pressor nerves would be expected to produce the largest fall in BP, while damage to mainly depressor fibers might even lead to a rise in BP after RDN. In consideration of this, identification of "ideal" ablation sites is highly attractive if the anatomy provides spatial compartmentalisation of these distinct afferent nerves, which remains unknown. Alternatively, there is genuinely a population of patients that do not respond or respond minimally and these need to be identified in the future.

It is possible to activate renal nerves non-invasively using a catheter placed in the renal artery. Sites in the renal artery that upon stimulation do not exert an acute BP rise (or even a BP fall) may reflect areas of convergence of sympatho-inhibitory (depressor) nerves, the ablation of which should ideally be avoided. In contrast, those sites at which stimulation results in a clear BP rise would be considered preferential ablation sites. Clearly, with unselected RDN the possibility of ablating sympatho-inhibitory (cold spot) or neutral (neutral spot) fibers seems likely and may counteract BP lowering effects achieved by ablating hot spots (33)(Figure 4).

Lu and colleagues reported that renal nerve stimulation promptly increased systolic BP >10 mmHg in both proximal and middle regions of the renal artery. However, during the stimulation of the distal portions of the renal artery, BP did not increase. Only the proximal

"responsive" sites ("hot spots") were ablated. As a result, targeted selective ablation not only prevented a similar BP response with stimulation at the previously responsive sites but also attenuated the response to stimulus at the ipsilateral mid-renal arterial sites, suggesting that surprisingly, afferents have a dominant role in BP reduction.

Recently, Tsioufis and colleagues reported the first-in-man study, in which 20 hypertensive patients underwent renal nerve stimulation (RNS) using the ConfidenHT™ system, a device created for this purpose. Bilateral stimulations were performed at 3 to 4 sites per artery at 2 and 4 mA. No peri-procedural adverse events occurred. Stimulation with 2 mA resulted in a maximum change of 8.3±6.3 mmHg in systolic BP (based on 119 stimulations; $p<0.001$) while stimulating with 4 mA resulted in a maximum variation of 10.1±7.8 mmHg (based on 61 stimulations; $p<0.001$). The mean increase in stimulus-evoked systolic BP did not vary between mid, distal or branch sites when stimulating at 2mA but was significantly higher at ostial (23±14 mmHg) than in non-ostial locations (9±7 mmHg) when stimulating at 4 mA ($p=0.003$). This suggests that RNS might help in optimizing treatment effect and selecting potential responders to renal sympathetic denervation (34).

The SPYRAL HTN-OFF and ON MED trials showed that a large sequence of ablated spots of renal nerves in the main renal artery and its branches by radiofrequency is effective and consistent in lowering BPin patients who are drug-naive or treated with antihypertensive medications. However, these findings do not oppose the concept of "hot spots," as the higher number of ablated sites may improve the chance of hitting a pressor spot. Moreover, the successful denervation through a single circular lesion in the renal artery promoted by the endovascular ultrasound used in RADIANCE-HTN SOLO suggests that interruption of the nerve in any segment of the renal artery may be sufficient to achieve denervation.

Indirect Testing via Reflex Responses: Whereas direct neural stimulation uses energy, reflex elicitation uses a physiological stimulus to excite the efferent renal sympathetic nerves, and, thus, reflex-mediated vasoconstriction before and after renal denervation is used to assess intervention success. In patients, renal sympathetic vasoconstriction has been shown in response to mental stress (35), head-up tilt (36), and lower body negative pressure (37), and recent reports of isometric handgrip exercise-driven renal vasoconstriction in patients undergoing renal denervation are promising.

Contrasting from direct neural stimulation, reflex elicitation is not painful and thus can be performed in conscious patients. It also assesses the integrity of the entire efferent limb of the renal sympathetic innervation, avoiding complexities arising from relationships between stimulation and denervation loci. However, this modality is unable to assess afferent denervation, and the repeatability of reflexes may be impacted by habituation, sensitization, and intraprocedural sedative and analgesic medications.

Passive Monitoring: Passive monitoring techniques detect spontaneous efferent renal sympathetic nerve activity or its downstream effects, which are attenuated after successful renal denervation. The classic example is renal norepinephrine spillover, which was used to demonstrate renal sympathoexcitation in hypertensive patients (38) and to validate renal denervation after the procedure in a small group of patients (32). Although renal norepinephrine spillover cannot be used broadly for intra-procedural monitoring, new technologies based on passive monitoring approaches are being developed. One early-stage device detects spontaneous renal sympathetic nerve traffic from within the renal artery lumen (Autonomix Medical, Doylestown, PA, USA). Additionally, to overcome the strong and confounding influence of autoregulatory mechanisms on traditional measures of renal vascular tone (39, 40), novel means of renal sympathetic vascular control are under investigation for intra-procedural feedback (39, 41, 42).

Unlike the other modalities, this approach does not require a stimulus-response profile, which is inherently time-consuming and challenging to reproduce. However, passive monitoring techniques are influenced by anything that changes renal sympathetic outflow, including patient anxiety, autonomic reflexes, and pharmacological agents used for analgesia and sedation.

Intra-procedural validation of adequate renal sympathetic and afferent nerve ablation is a continuing challenge to the field of renal denervation. Efforts to translate direct neural stimulation, reflex elicitation, and passive monitoring techniques into clinical technologies have considerable momentum. Interventionalists equipped with such technologies may be able to perform renal denervation with meaningful feedback, maximizing the efficacy and safety of this promising therapy.

Do renal nerves regrow following RDN?

Booth and colleagues reported that in sheep, functional re-innervation was demonstrated by the finding that electrical stimulation of the whole renal nerve resulted in normal afferent (increase in mean BP and fall in heart rate) and efferent responses (decreases in renal vascular conductance and renal blood flow), in contrast to the lack of responses acutely post-RDN (Figure 5) (43).

Anatomical and biochemical studies indicated that 1 week after catheter-based RDN, the renal levels of markers for sympathetic efferent nerves (tissue noradrenaline and immunohistochemistry for tyrosine hydroxylase) and afferent sensory nerves (immunohistochemistry for calcitonin gene-related peptide) were significantly reduced, but by 11 months post-RDN the levels had returned to normal in sheep, indicating reinnervation of both the sensory afferent nerves and the sympathetic efferent nerves (43). It is currently

unknown whether the control of the renal vasculature, renin release and sodium excretion in response to changes in RSNA is normal in the re-innervated kidney and whether there are changes in the central pathways controlling RSNA following RDN.

Conversely, Mauriello and colleagues reported evidence of neural sprouting as early as five months after kidney transplantation, rising in association with clinical hypertension; in all likelihood, nerve sprouting stems from sympathetic ganglia since neural regeneration appears to be limited to sympathetic efferent fibers only. Complete peri-adventitial nerve regeneration in hypertensive subjects to reach levels in native arteries, being paralleled by worsening of hypertension-related lesions in distal arterioles, seems to be achieved within 24 months following transplantation. Indeed, nerve density in kidney transplant arteries tends to reach levels similar to those in native arteries (44).

Re-innervation in humans following catheter-based RDN has not been demonstrated, which lead us to think about possible mechanisms capable of translating a sustained decrease in BP despite re-innervation; these may include decreased intrarenal levels of renin, reduced RSNA burst size and burst incidence, owing to changes in central autonomic nuclei.

Methods to predict Responders and Non-Responders to RDN

Efforts to recognize patient features that predict the BP response to RDN has mostly relied on post-hoc analyses of data from studies assessing the impact of RDN in a broad range of drug-resistant hypertensive subjects. This has been done either by matching the magnitude of BP response in different groups of individuals (or by classifying them as “responders” or “non-responders” to RDN and then comparing the baseline characteristics of the individuals in the two groups. The lack of substantial parameters able to predict the response of BP fall to RDN turned it into a constant quest for clinicians and interventionists (45, 46). Aspects

contributing to the variability of BP response to RDNinclude technical issues with the procedure itself or the measurement of BP, baseline patient physical characteristics, and concomitant anti-hypertensive treatments. We suggest that these have all contributed to confusing any analysis of predicting relaible indicators of respnding patients.

Clinical parameters: Changes in the office BP or ABPM are appropriate endpoints for clinical trials. However, individual BP response may be a poor indicator of so-called therapy responders, due to significant within-patient variability on both office and ambulatory blood pressure measurements. Kandzari and colleagues performed a multivariable analysis of the participants in the Symplicity HTN-3 trial, identifying predictors of responsiveness to RDN such as baseline office SBP ≥180 mmHg, aldosterone antagonist use, non-use of vasodilators, and the quantity of ablated spots (6). However, high baseline BP seems to be the only *consistent* predictor of response in RDN trials and this is not unique to RDN. Recently, the SPYRAL HTN-OFF MED reported that the higher baseline heart rate was associated with higher BP decrease, which may indicate that RDN works better in patients with higher sympathetic to vagal balance (assessed in the absence of interfering drugs) (13). In contrast, isolated systolic hypertension was associated with lower pressure responses than combined hypertension in unmatched post hoc sub-analyses (47), possibly reflecting a more significant "fixed" structural component to this type of hypertension.

The potential role of Inflammatory Pathways: There is much evidence that inflammation of the vasculature, brain, and kidneys contributes to chronic increases in BP (48-50). Some studies propose that renal inflammation specifically may be directly triggered by amplified renal nerve activity (REF).Recently, a study reported that angiotensin II (AngII)-induced

hypertension in mice is decreased by RDN and that this is paralleled by reduced renal inflammation, which was independent of the BP decrease (51). Since specific ablation of renal afferent nerves had no effect on the pathogenesis of hypertension in this study, it was settled that the antihypertensive effect of RDN was due to ablation of efferent renal nerve-mediated renal inflammation (51). Similarly, Banek and colleagues also reported that RDN attenuates hypertension and renal inflammation in the rat deoxycorticosterone acetate (DOCA)-salt model (52). Importantly, they also stated that resting afferent nerve discharge is elevated in DOCA-salt rats and that this is caused by an increase in certain inflammatory cytokines in the kidney (52). Another finding by Banek and colleagues was that afferent-specific renal nerve ablation attenuated the development of hypertension in this model to the same degree as total RDN (52). They concluded that even though renal inflammation may have its onset in efferent renal nerves, hypertension was driven by augmented afferent renal nerve traffic, probably secondary to renal inflammation (52). A subsequent study from the same group demonstrated that, afferent-specific renal nerve ablation also decreased arterial pressure in the established phase of DOCA-salt hypertension to the same degree as total RDN (53). However, neither method of ablation reversed renal inflammation in the established phase of this model suggesting other drivers for the inflammation.

Even though there is a shortage of clinical studies directly measuring renal inflammation after RDN, there are several studies in which peripheral inflammation was evaluated. Kampmann and colleagues reported similar cardiovascular and inflammatory responses in hypertensive humans that underwent catheter-based RDN, where all measured circulating inflammatory cytokines (TNF-α, IL-6, and IL-1β) remained unaffected six months post-treatment, despite a significant decrease in arterial pressure (54). In contrast to these results, a clinical report from Zaldivia and colleagues (55) described a reduction in circulating inflammatory cytokines (MCP-1, IL-1β, TNF-α, and IL-12) several months after catheter-based RDN in hypertensive

subjects. Further clinical and preclinical investigations are necessary to elucidate the anti-inflammatory effect of RDN.

Drug Interactions

The recent three sham-controlled trials SPYRAL HTN-OFF MED and RADIANCE SOLO in which patients were not on concurrent medication, and SPYRAL HTN-ON MED in which 29% of individuals were using one drug, 18% were taking two pills, and 53% were using 3 types of antihypertensive medications (distributed as follows: ~60% thiazide diuretic, ~75% calcium channel blockers, ~85% ACE-I/ARB, and only ~15% were taking beta-blockers; no patient was prescribed clonidine or spironolactone) presented a significant baseline-adjusted fall in ambulatory BP, even though background treatment and baseline BP levels differed between them: SPYRAL HTN-ON MED: 24-hour systolic BP (SBP), − 7.0 mm Hg (95% confidence interval [CI], − 12.0 to − 2.1; P =0.0059), 24-hour diastolic BP, − 4.3 mm Hg (95% CI, – 7.8 to – 0.8; P =0.0174); RADIANCE-HTN SOLO: 24-hour SBP, – 7.0 ± 8.6 mm Hg; P =0.006, 24-hour diastolic BP, – 4.4 ± 5.8 mm Hg; P =0.07; and SPYRAL HTN-OFF MED: 24-hour SBP, – 5.3 mm Hg (95% CI, − 8.6 to – 2.0; P =0.0020), 24-hour diastolic BP, – 4.8 mm Hg (95% CI, – 6.8 to – 2.8; P =0.001. Moreover, the effect in drug naïve patients seems similar when comparing SPYRAL HTN-OFF MED with RADIANCE-HTN SOLO. Further studies are needed to elucidate if spironolactone and or clonidine cause any drug interaction with RDN or if their response can predict responders to RDN.

Potential Impact on CV outcomes

Reduction in target organ damage by a treatment intervention is closely linked to a decrease in time-averaged BP it causes. In a meta-analysis including 613,815 patients from

122 studies, reduction of office BP by 10mmHg was related to the reduction of cardiovascular events by 20%, overall mortality by 13%, coronary artery disease by 17%, strokes by 27% and heart failure by 28%, respectively (56). In the HOPE-3 study, patients with baseline office BP more than 143.5mmHg had a reduction of BP by -5.8/-3.0mmHg (due to pharmacologic therapy) associated with a 28% lower incidence of cardiovascular events compared with the placebo group (57).

Even though not proven by a prospective outcome trial we predict that a 10mmHg decrease in office BP achieved in RDN trials, if maintained long-term, would be associated with a reduction in cardiovascular events by ~25%, especially heart failure and stroke.

Summary

The positive results from SPYRAL HTN-OFF MED, RADIANCE SOLO, and SPYRAL HTN-ON MED signify a new beginning for the RDN field. However, several unsolved issues remain, including identification of those patients who may benefit most, defining the durability of effects on BP and safety in the long-term, determining the mechanisms underpining the RDN evoked fall in BP in order to optimise response, and developing tests/technologies to establish the extent of renal artery denervation at the time of intervention as well more complete ablation.

Filling in these blanks will help to advance the field further, design approaches to amplify the BP lowering response and ultimately determine the clinical utility of RDN. Here, we have summarized some of the most relevant issues identified by a group of clinical and experimental scientist to facilitate this critical task.

Acknowledgments

FM is supported by Deutsche Gesellschaft für Kardiologie, Deutsche Hochdruckliga, and Deutsche Forschungsgemeinschaft (SFB TRR 219), and has received grant support and personal fees from Medtronic and Recor Medical.

MPS is supported by an NHMRC Research Fellowship and has received consulting fees, and/or travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer and Boehringer-Ingelheim.

JFRP was supported by the British Heart Foundation (UK) and the Health Research Council of New Zealand.

References

1. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373(9671):1275-81.
2. Symplicity HTNI, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376(9756):1903-9.
3. Donazzan L, Mahfoud F, Ewen S, Ukena C, Cremers B, Kirsch CM, et al. Effects of catheter-based renal denervation on cardiac sympathetic activity and innervation in patients with resistant hypertension. Clin Res Cardiol. 2016;105(4):364-71.
4. Hering D, Marusic P, Walton AS, Lambert EA, Krum H, Narkiewicz K, et al. Sustained sympathetic and blood pressure reduction 1 year after renal denervation in patients with resistant hypertension. Hypertension. 2014;64(1):118-24.
5. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393-401.
6. Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J. 2015;36(4):219-27.
7. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet. 2015;385(9981):1957-65.

8. Azizi M, Pereira H, Hamdidouche I, Gosse P, Monge M, Bobrie G, et al. Adherence to Antihypertensive Treatment and the Blood Pressure-Lowering Effects of Renal Denervation in the Renal Denervation for Hypertension (DENERHTN) Trial. Circulation. 2016;134(12):847-57.
9. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, et al. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. J Am Coll Cardiol. 2014;63(8):834-5.
10. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31(4):766-74.
11. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100(11):855-61.
12. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018;391(10137):2346-55.
13. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017;390(10108):2160-70.
14. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018;391(10137):2335-45.
15. Schlaich MP, Kiuchi MG, Esler MD. Renal Denervation-Ready for Prime Time!? The Steep SPYRAL Stairs to RADIANCE in Hypertension Treatment. Hypertension. 2018;72(2):287-90.
16. Johns EJ, Kopp UC, DiBona GF. Neural control of renal function. Compr Physiol. 2011;1(2):731-67.
17. DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. Am J Physiol-Reg I. 2010;298(2):R245-R53.
18. Foss JD, Fink GD, Osborn JW. Reversal of Genetic Salt-Sensitive Hypertension by Targeted Sympathetic Ablation. Hypertension. 2013;61(4):806-+.
19. Jacob F, Ariza P, Osborn JW. Renal denervation chronically lowers arterial pressure independent of dietary sodium intake in normal rats. Am J Physiol-Heart C. 2003;284(6):H2302-H10.
20. Jacob F, LaBine BG, Ariza P, Katz SA, Osborn JW. Renal denervation causes chronic hypotension in rats: Role of beta(1)-adrenoceptor activity. Clin Exp Pharmacol P. 2005;32(4):255-62.
21. Foss JD, Fink GD, Osborn JW. Differential role of afferent and efferent renal nerves in the maintenance of early- and late-phase Dahl S hypertension. Am J Physiol-Reg I. 2016;310(3):R262-R7.
22. Guertzenstein PG, Silver A. Fall in blood pressure produced from discrete regions of the ventral surface of the medulla by glycine and lesions. J Physiol. 1974;242(2):489-503.
23. Tsai WC, Chan YH, Chinda K, Chen Z, Patel J, Shen C, et al. Effects of renal sympathetic denervation on the stellate ganglion and brain stem in dogs. Heart Rhythm. 2017;14(2):255-62.
24. Bramlett HM, Dietrich WD. Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. Prog Brain Res. 2007;161:125-41.
25. Meckler RL, Weaver LC. Comparison of the distributions of renal and splenic neurons in sympathetic ganglia. J Auton Nerv Syst. 1984;11(2):189-200.
26. Sripairojthikoon W, Wyss JM. Cells of origin of the sympathetic renal innervation in rat. Am J Physiol. 1987;252(6 Pt 2):F957-63.
27. Gattone VH, 2nd, Marfurt CF, Dallie S. Extrinsic innervation of the rat kidney: a retrograde tracing study. Am J Physiol. 1986;250(2 Pt 2):F189-96.
28. Ferguson M, Ryan GB, Bell C. Localization of sympathetic and sensory neurons innervating the rat kidney. J Auton Nerv Syst. 1986;16(4):279-88.

29. Pilowsky P, Llewellyn-Smith IJ, Minson J, Chalmers J. Sympathetic preganglionic neurons in rabbit spinal cord that project to the stellate or the superior cervical ganglion. Brain Res. 1992;577(2):181-8.
30. Campese VM, Kogosov E. Renal afferent denervation prevents hypertension in rats with chronic renal failure. Hypertension. 1995;25(4 Pt 2):878-82.
31. Jansen AS, Wessendorf MW, Loewy AD. Transneuronal labeling of CNS neuropeptide and monoamine neurons after pseudorabies virus injections into the stellate ganglion. Brain Res. 1995;683(1):1-24.
32. Esler M. Illusions of truths in the Symplicity HTN-3 trial: generic design strengths but neuroscience failings. J Am Soc Hypertens. 2014;8(8):593-8.
33. Fudim M, Sobotka AA, Yin YH, Wang JW, Levin H, Esler M, et al. Selective vs. Global Renal Denervation: a Case for Less Is More. Current Hypertension Reports. 2018;20(5).
34. Tsioufis KP, Feyz L, Dimitriadis K, Konstantinidis D, Tousoulis D, Voskuil M, et al. Safety and performance of diagnostic electrical mapping of renal nerves in hypertensive patients. EuroIntervention. 2018.
35. Ray CA, Carter JR. Effects of aerobic exercise training on sympathetic and renal responses to mental stress in humans. Am J Physiol Heart Circ Physiol. 2010;298(1):H229-34.
36. Conboy EE, Fogelman AE, Sauder CL, Ray CA. Endurance training reduces renal vasoconstriction to orthostatic stress. Am J Physiol Renal Physiol. 2010;298(2):F279-84.
37. Hansen JM, Abildgaard U, Fogh-Andersen N, Kanstrup IL, Bratholm P, Plum I, et al. The transplanted human kidney does not achieve functional reinnervation. Clin Sci (Lond). 1994;87(1):13-20.
38. Esler M, Jennings G, Lambert G. Noradrenaline release and the pathophysiology of primary human hypertension. Am J Hypertens. 1989;2(3 Pt 2):140S-6S.
39. Schiller AM, Pellegrino PR, Zucker IH. Eppur Si Muove: The dynamic nature of physiological control of renal blood flow by the renal sympathetic nerves. Auton Neurosci. 2017;204:17-24.
40. Carlstrom M, Wilcox CS, Arendshorst WJ. Renal autoregulation in health and disease. Physiol Rev. 2015;95(2):405-511.
41. Pellegrino P, Schiller AM, Wang H, Chatzizisis Y, Zucker I. Functional renal denervation decreases renal vascular control quantifiedby pressure-flow monitoring in swine. ACC18; March 20, 2018; Orlando, Florida. Journal of the American College of Cardiology

Journal of the American College of Cardiology

2018. p. A1179.
42. Finegold J, Broyd C, Shun-shin M, Petraco R, De Silva R, Francis D, et al. Systematic evaluation of haemodynamic parameters to predict haemodynamic responders to renal artery denervation. Euro PCR 2016; 6 May 2016; Paris, France. EuroIntervention: EuroIntervention; 2016.
43. Booth LC, Nishi EE, Yao ST, Ramchandra R, Lambert GW, Schlaich MP, et al. Reinnervation of renal afferent and efferent nerves at 5.5 and 11 months after catheter-based radiofrequency renal denervation in sheep. Hypertension. 2015;65(2):393-400.
44. Mauriello A, Rovella V, Borri F, Anemona L, Giannini E, Giacobbi E, et al. Hypertension in kidney transplantation is associated with an early renal nerve sprouting. Nephrol Dial Transplant. 2017;32(6):1053-60.
45. Wang Y. It is urgent to investigate predictors of the response of blood pressure to renal denervation. Can J Cardiol. 2014;30(4):465 e7.
46. Donazzan L, Ewen S, Bohm M. Until questions on intraprocedural efficacy control, renal nerve distribution and predictors of BP response are answered, the interpretation of clinical trials on renal denervation will remain uncertain. Evid Based Med. 2014;19(6):227-8.
47. Mahfoud F, Bakris G, Bhatt DL, Esler M, Ewen S, Fahy M, et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. Eur Heart J. 2017;38(2):93-100.

48. De Miguel C, Rudemiller NP, Abais JM, Mattson DL. Inflammation and hypertension: new understandings and potential therapeutic targets. Curr Hypertens Rep. 2015;17(1):507.
49. McMaster WG, Kirabo A, Madhur MS, Harrison DG. Inflammation, immunity, and hypertensive end-organ damage. Circ Res. 2015;116(6):1022-33.
50. Zubcevic J, Santisteban MM, Pitts T, Baekey DM, Perez PD, Bolser DC, et al. Functional neural-bone marrow pathways: implications in hypertension and cardiovascular disease. Hypertension. 2014;63(6):e129-39.
51. Xiao L, Kirabo A, Wu J, Saleh MA, Zhu L, Wang F, et al. Renal Denervation Prevents Immune Cell Activation and Renal Inflammation in Angiotensin II-Induced Hypertension. Circ Res. 2015;117(6):547-57.
52. Banek CT, Knuepfer MM, Foss JD, Fiege JK, Asirvatham-Jeyaraj N, Van Helden D, et al. Resting Afferent Renal Nerve Discharge and Renal Inflammation: Elucidating the Role of Afferent and Efferent Renal Nerves in Deoxycorticosterone Acetate Salt Hypertension. Hypertension. 2016;68(6):1415-23.
53. Banek CT, Gauthier MM, Baumann DC, Van Heiden D, Asirvatham-Jeyaraj N, Panoskaltsis-Mortari A, et al. Targeted afferent renal denervation reduces arterial pressure but not renal inflammation in established DOCA-salt hypertension in the rat. Am J Physiol-Reg I. 2018;314(6):R883-R91.
54. Kampmann U, Mathiassen ON, Christensen KL, Buus NH, Bjerre M, Vase H, et al. Effects of Renal Denervation on Insulin Sensitivity and Inflammatory Markers in Nondiabetic Patients with Treatment-Resistant Hypertension. J Diabetes Res. 2017;2017:6915310.
55. Zaldivia MT, Rivera J, Hering D, Marusic P, Sata Y, Lim B, et al. Renal Denervation Reduces Monocyte Activation and Monocyte-Platelet Aggregate Formation: An Anti-Inflammatory Effect Relevant for Cardiovascular Risk. Hypertension. 2017;69(2):323-31.
56. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-67.
57. Yusuf S, Lonn E, Pais P, Bosch J, Lopez-Jaramillo P, Zhu J, et al. Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease. N Engl J Med. 2016;374(21):2032-43.
58. Mompeo B, Maranillo E, Garcia-Touchard A, Larkin T, Sanudo J. The gross anatomy of the renal sympathetic nerves revisited. Clin Anat. 2016;29(5):660-4.
59. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. J Am Coll Cardiol. 2014;64(7):635-43.

Figures

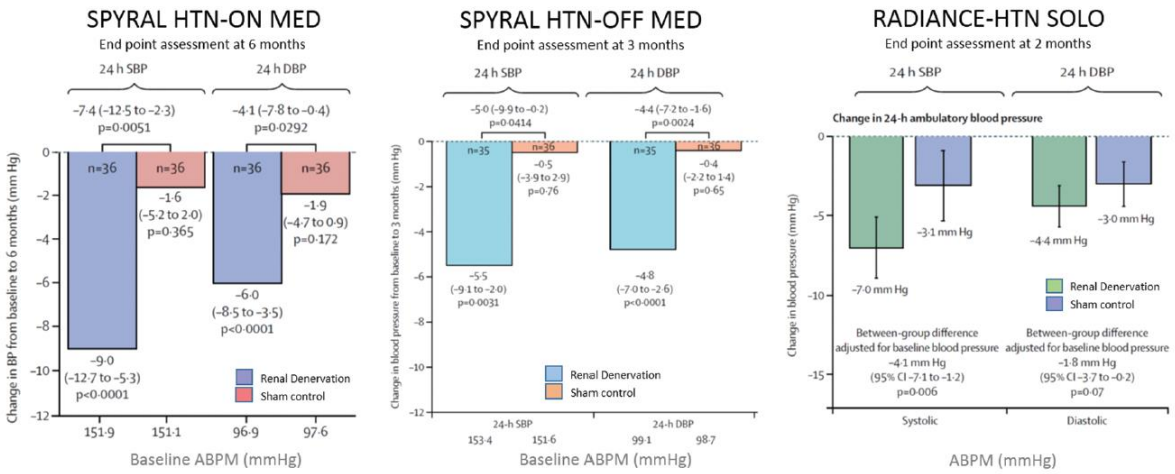

Figure 1. Comparison 24-h systolic and diastolic blood pressure (SBP and DBP) changes in renal denervation *vs.* sham-control groups in the 3 recent randomized, sham-controlled clinical trials. ABPM indicates ambulatory BP monitoring; CI, confi dence interval; HTN-ON MED, Spyral Hypertension on Medication trial; HTN-OFF MED, Spyral Hypertension OFF Medication trial; and RADIANCE-HTN SOLO, RADIANCE hypertension solo (off medication) trial. Reprinted from Kandzari et al, 1 Azizi et al, 2 and Townsend et al 3 with permission.

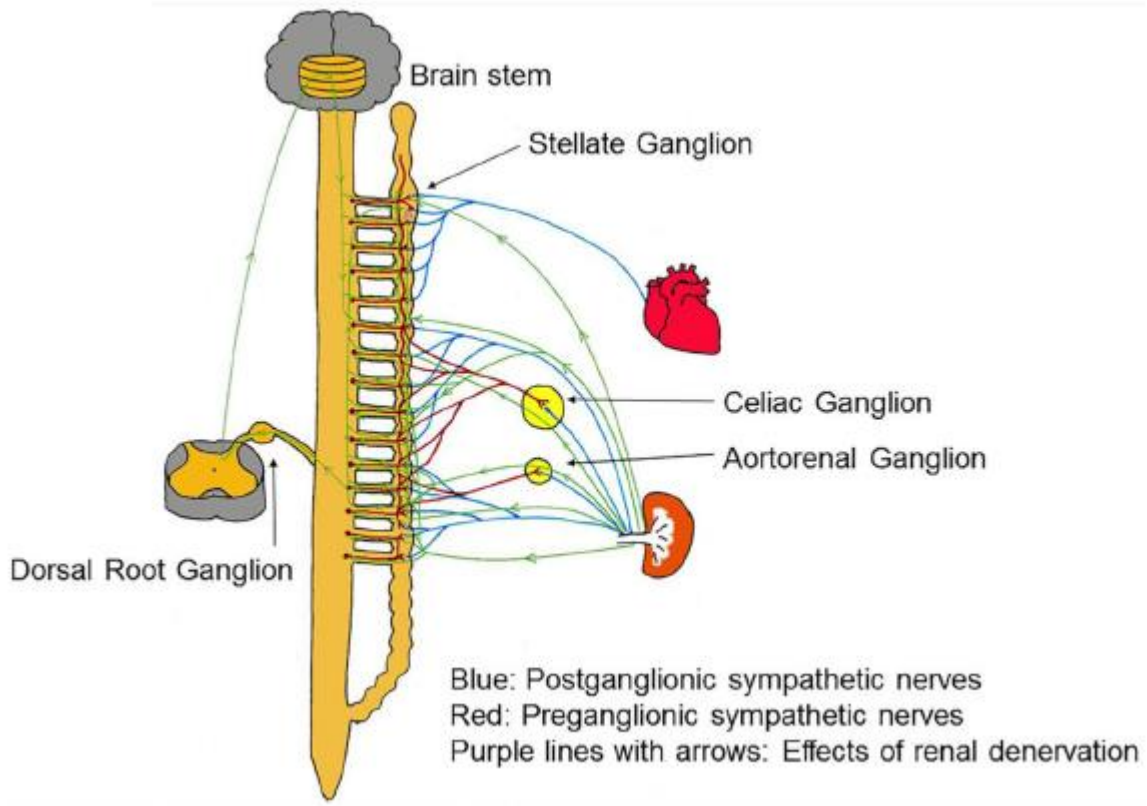

Figure 2. There are multiple pathways to connect renal sympathetic nerves with the stellate ganglion. Both preganglionic and postganglionic sympathetic fibers may innervate the renal artery, according to the representation of possible connections among different nerve structures.

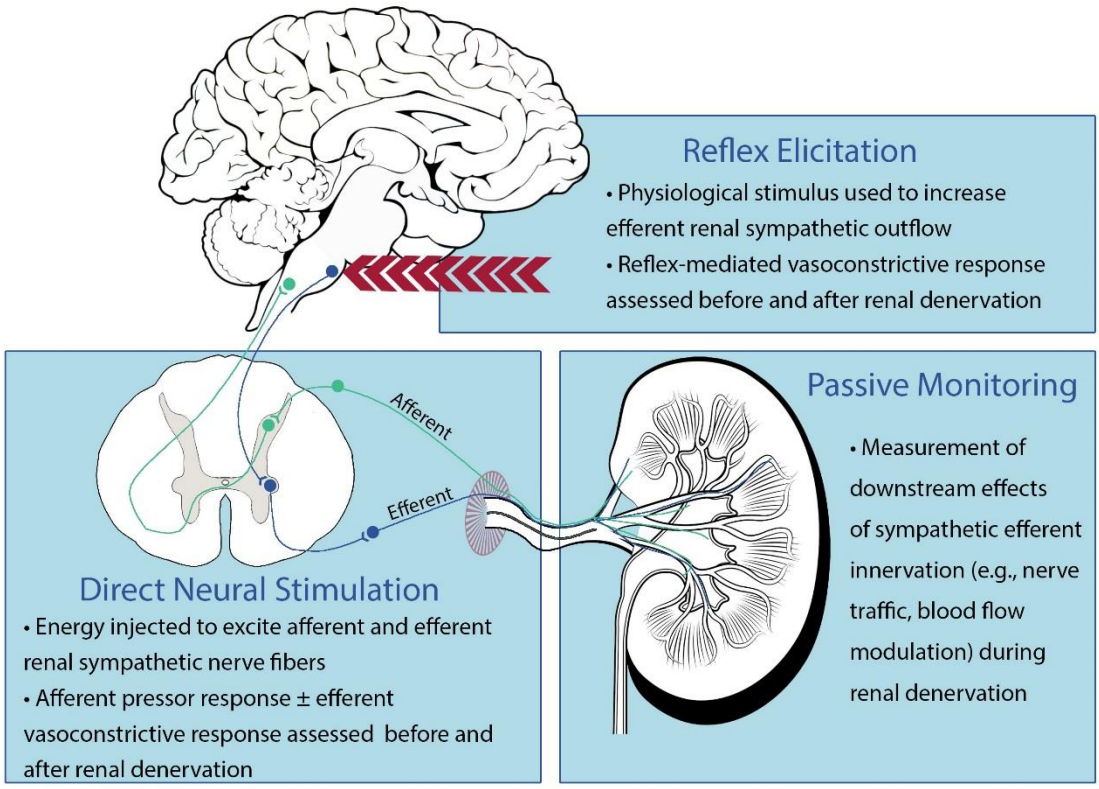

Figure 3. The promising three modalities of procedural monitoring (direct neural stimulation, reflex elicitation, and passive monitoring) evaluated by new technologies, providing intra-procedural validation of renal denervation.

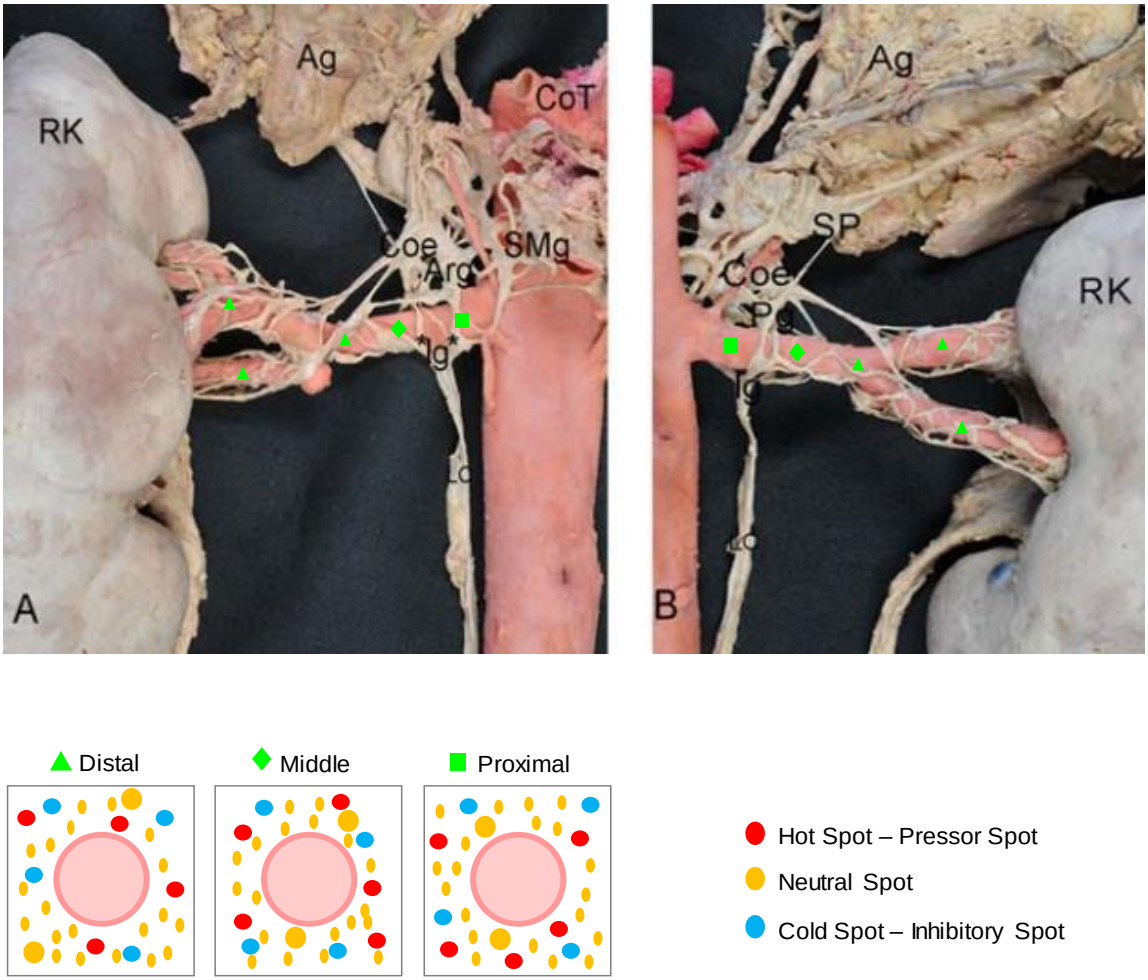

Figure 4. The top picture shows the right renal artery sympathetic innervation in (A) anterior and (B) posterior views divided in three segments: proximal (green square), middle (green lozenge), and distal (green triangle) . The bottom illustration depicts a schematic concept for selective *vs.* global renal denervation: red dots represent "hot spots" - pressor spots. These are nerves that when stimulated increase blood pressure. They are the ideal target of renal denervation. Blue dots represent "cold spots" - inhibitory spots, which lower blood pressure when stimulated. The yellow dots represent the majority of nerve fibers, which are neutral in their contribution for blood pressure physiology and do not show hemodynamic effects when stimulated. Ag (adrenal gland), Arg (aorticorenal ganglion), Coe (coeliac ganglion), CoT (coeliac trunk), Ig (renal inferior ganglion), LC (contribution of the lumbar chain to the renal plexus), Pg (renal posterior ganglion), RK (right kidney), SMg (superior mesenteric ganglion), SP (Thoracic splanchnic nerves), * (connection between ganglia). Adapted from (58)Mompeo et al. Clinical Anatomy 2016; 29:660–664, (59) Sakakura et al. Journal of the American College of Cardiology 2014; 64:635–43, and (33) Fudim et al. Current Hypertension Reports 2018; 20:37.

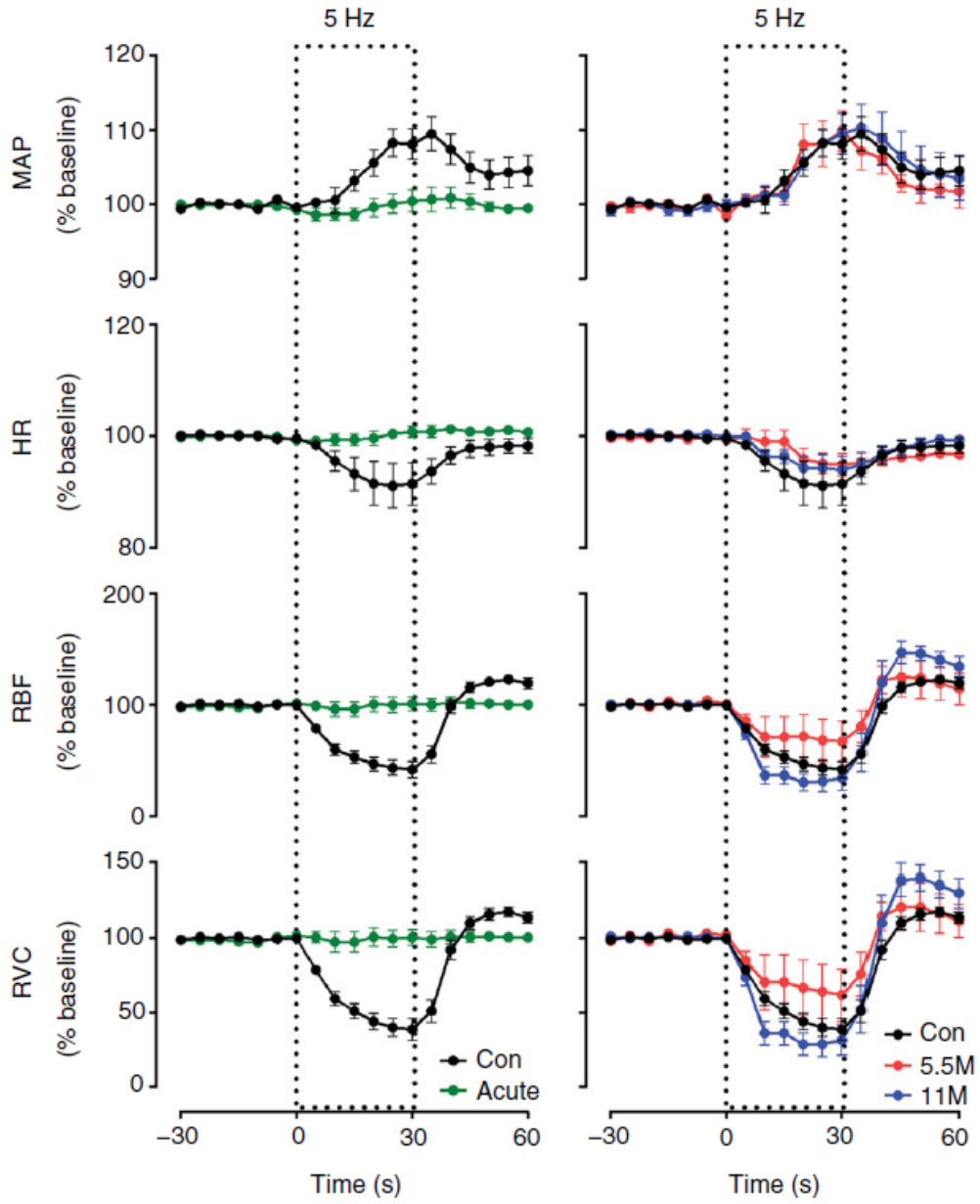

Figure 5. Effects of electrical stimulation (5 Hz, 10 V, from 0 to 30 s) of the whole renal nerve on mean arterial pressure (MAP), heart rate (HR), renal vascular conductance (RVC) and renal blood flow (RBF) in normotensive anaesthetized sheep. Left panel shows results for control non-denervated sheep (black, n = 6) and acutely denervated sheep (green, n = 6). Right panel shows results for control non-denervated sheep (black, n = 6), 5.5 months postdenervation (red, n = 6) and 11 months postdenervation (blue, n = 5). Data are 5 s averages ± SEM (43).