Journal of Human Hypertension (2019) 33:716–724
https://doi.org/10.1038/s41371-019-0244-5

REVIEW ARTICLE

Selective renal denervation guided by renal nerve stimulation: mapping renal nerves for unmet clinical needs

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Received: 30 December 2018 / Revised: 10 July 2019 / Accepted: 29 July 2019 / Published online: 2 September 2019
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Abstract

Renal denervation (RDN) is a well-known innovative therapy for hypertension. However, the effects of global RDN on blood pressure (BP) lowering are quite variable. Insufficient and futile denervation is considered a major factor contributing to the variable results. Mapping renal nerves by renal nerve stimulation (RNS) is the most promising technique to improve the efficacy of RDN. We summarize the clinical and experimental data available regarding RNS-guided RDN and explain the roles of renal efferent nerves, afferent nerves and vagal nerves in BP changes. We further identify five different BP response patterns to RNS and provide an explanation of the underlying neuroanatomical basis.

Introduction

Renal denervation (RDN) has been applied to treat drug-resistant hypertension. However, the effects of RDN on blood pressure (BP) reduction have been inconsistent. Initial studies without a sham control showed significant BP reduction in hypertension, but disappointingly, SYMPLICITY HTN-3, which was first introduced to a sham group failed to meet its primary efficacy endpoint. As a result, the efficacy of RDN for BP lowering was challenged. However, several trials reconfirmed BP reduction after RDN with statistical significance after SYMPLICITY HTN-3. Futile renal nerve damage is proposed to be a critical factor contributing to these variable results [1]. Recently, RDN guided by renal nerve stimulation (RNS) has been believed to be helpful for finding sympatho-stimulatory sites and avoiding sympatho-inhibitory sites, thus improving the efficacy of renal nerve damage [2]. Thus, we performed this review to summarize the advances in clinical and experimental data regarding RNS-guided RDN in recent years.

Insufficient and futile denervation is considered a major factor contributing to the variable results of RDN

The early SYMPLICITY HTN trials demonstrated a substantial and sustained BP reduction after RDN. The HTN-1 [3] study showed that the average office BP was decreased by 22/11 mmHg and 27/17 mmHg at 6 and 12 months. In HTN-2 [4], 106 patients were randomly assigned to a group undergoing RDN or to a control group. Global denervation was applied in the RDN group, while the control group was only treated with antihypertensive drugs. A significant reduction in office BP by 32/12 mmHg at 6 months [4] and 28/18 mmHg at 12 months [5] was demonstrated in the RDN group, whereas the BP remained unchanged in the control group. When the primary endpoint was met, some patients in the control group also received RDN. The office SBP of these patients was reduced from 199 to 166 mmHg 6 months later [5]. HTN-3 [6] was the first sham-controlled clinical trial in the RDN field. To avoid the white coat effect, 24 h ambulatory BP

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was used as the primary endpoint. Disappointingly, the results failed to demonstrate a significant BP lowering effect. Serious concerns were raised, and it was even questioned whether it was necessary to develop RDN further. Based on these concerns and questions, researchers performed a subgroup analysis of HTN-3 and conducted new studies to investigate contributors to the negative findings. Surprisingly, differing from HTN-3, these new studies [7–12] again demonstrated BP reduction after RDN. Moreover, investigators have realized several serious limitations of HTN-3, such as a lack of experience of the RDN operators, confounders of antihypertensive drug changes during the study, and the absence of indexes to indicate successful procedural endpoints.

The results of the subgroup analysis of HTN-3 [13] indicated that BP was significantly decreased in patients once more than 12 or 13 ablations for each side of the renal artery were performed. The positive correlation between BP reduction and the number of ablation points suggested that adding more ablation points can increase the probability of denervating renal nerves. Prochnau [14] treated 10 nonresponders, defined as patients with a <10 mmHg reduction in SBP after the first RDN using high radiofrequency again with cryoenergy for RDN. Significant reductions in both office and ambulatory BP were observed. Similar results were reported by Kaiser [15]. Eight patients who were deemed nonresponders to the first radiofrequency ablation underwent another radiofrequency ablation, and 63% of the patients had a further BP reduction of more than 10 mmHg at 6 months. A redo procedure further lowered the BP, indicating that incomplete denervation might be a critical contributor to the lack of BP reduction efficacy after RDN. The RADIOSOUND-HTN study [16] compared the differences between different therapeutic strategies of RDN. Patients with resistant hypertension were randomized to receive radiofrequency RDN of the main renal arteries (RFM-RDN), radiofrequency RDN for additional side branch ablation (RFB-RDN), or endovascular ultrasound-based RDN of the main renal artery (USM-RDN). After 3 months, the systolic daytime ambulatory BP decreased by 6.5 mmHg in the RFM-RDN group, 8.3 mmHg in the RFB-RDN group, and 13.2 mmHg in the USM-RDN group. Ultrasound-based RDN can reach 6–7 mm in depth to the tissue from the lumen, while the low energy radiofrequency RDN can only reach 3 mm. Thus, ultrasound-based RDN can affect more renal nerves. This finding further strengthened the concept that more complete denervation would result in a better efficacy of denervation. Therefore, ensuring that a sufficient number of sympathetic nerves are destroyed during the procedure is crucial.

Patients with office systolic BP drops of 10 mmHg or less were defined as no-responders in HTN-1 and HTN-2 [3–5, 17]. Reviewing the two studies, 15–21% patients were recognized as nonresponders at 12 months. A Swedish registry study [9] showed that both office and ambulatory BP were decreased at 6 months (office BP decreased by 15/6 mmHg and ambulatory BP decreased by 8/7 mmHg). However, 33% of patients were still considered nonresponders in this study. In the DENERHTN [7], 106 patients were randomized to the stepped-care antihypertensive treatment (SSAHT) group or the SSAHT plus RDN group. At 6 months, the ambulatory SBP in the daytime decreased by 9.9 mmHg in the SSAHT group and by 15.8 mmHg in the SSAHT plus RDN group. Notably, the variability in the BP reductions of the SSAHT plus RDN group was greater than that of the SSAHT group. This result indicates that some patients in the SSAHT plus RDN group exhibited greater BP reduction.

To rule out the confounder of medications, the SPYRAL HTN-OFF MED study [18] confirmed that RDN can reduce BP in the absence of antihypertensive drugs and established the biological and net effects of RDN on hypertension. Eighty eligible hypertension patients without antihypertensive therapy were included. In contrast to the SYMPLICITY HTN series, investigators only performed four to six discrete ablations along the bilateral main renal arteries. The investigators of the SPYRAL HTN-OFF MED study targeted whole arteries, including the main renal arteries, branch arteries and accessory arteries. After 3 months, patients in the RDN group had a significant reduction in both office and ambulatory BP, and no significant changes were observed in the sham group. The intergroup difference was 5.0/4.4 mmHg in ambulatory BP and 7.7/4.9 mmHg in office BP. However, a total of 43.8 ablations were attempted, while 17.9 and 25.9 ablations targeted the main and branch arteries, respectively. Even with the radical ablation strategy, the BP reduction was moderate. In addition, 32.4% of the patients in the RDN group had a reduction of less than 10 mmHg in office SBP, and 40% of the patients had a reduction of <5 mmHg in ambulatory BP. According to Prochnau [14], ~30–40% of treated patients were nonresponders. Some patients who were supposed to have BP reduction failed to demonstrate a reduction and even exhibited an augmented BP. As shown in Fig. 1, 28% and 20% of patients had increases in ambulatory SBP and DBP, respectively. Because of the different BP responses, we hypothesized that heterogeneous fibers exist in renal nerves, which may lead to different BP responses to RDN and offset each other. SPYRAL HTN-ON MED [12] further proved the efficacy of RDN on patients with rigid antihypertensive drug regimens and drug surveillance. The number of ablations and the procedural technique were similar to those in the SPYRAL HTN-OFF MED study. Office BP dropped by 9.4/5.2 mmHg, and the 24 h ambulatory BP dropped by

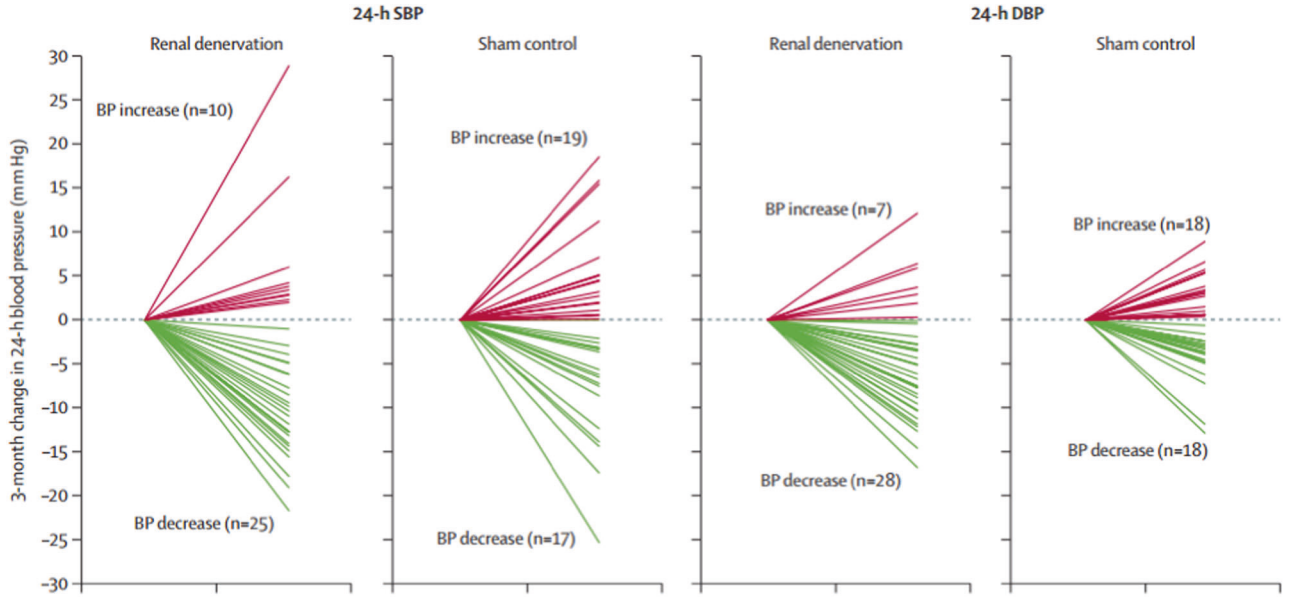

Fig. 1 Changes at 3 months in individual patients in the SPYRAL HTN-OFF MED study

9.0/6.0 mmHg at 6 months in the RDN group; by contrast, the office BP dropped by 2.6/1.7 mmHg and the 24 h ambulatory BP dropped by 1.6/1.9 mmHg in the sham group. Similar to the results of SPYRAL HTN-OFF MED, despite global RDN with a radical ablation strategy, the BP reduction was still moderate and could not lead to BP reduction in all patients. This finding suggests that global denervation is futile in some sites and that only increasing nontargeted ablations cannot improve the limitations of global ablation. Tsioufis [10] mentioned that the lack of an intraprocedural predictor of effective RDN could be the main reason for this problem.

It has been reported that ^{123}I-mIBG uptake and washout were used as parameters of renal sympathetic activity [19]. Patients whose ambulatory BP remained unchanged after RDN also had no significant reduction in renal sympathetic activity. Historical observations have shown that surgical sympathectomy can significantly reduce sympathetic activity, whereas catheter-based RDN cannot achieve the same effects as surgical sympathectomy. HTN-1 showed that RDN reduces renal noradrenaline spillover by only 47% [3], and this reduction has been considered inadequate.

Although the reasons why BP increases instead of falling in some patients undergoing RDN are not fully clarified, ablating more sympatho-stimulatory fibers and avoiding the ablation of sympatho-inhibitory fibers should be very important. Nontargeted ablation and lack of a functional procedural endpoint might be the main causes of futile denervation. Therefore, developing a simple, reproducible technology to guide denervation is an urgent clinical unmet need.

Mapping renal nerves by renal electrical stimulation technique for selective RDN

Previous studies referring to atrial vagal denervation to treat atrial fibrillation indicated that electrical stimulation can help to detect vagus plexus. Inspired by the concept, Pokoshalov et al. [20] first introduced electrical stimulation technology into the RDN field in patients with arrhythmia and hypertension in 2012. In 2013, Chinushi et al. [21] electrically stimulated the nerves surrounding renal arteries before and after RDN in a canine model. RNS in the proximal portion of the renal artery increased the BP from 146/89 to 170/103 mmHg before RDN. However, only a minimal increase from 150/90 to 152/92 mmHg was observed when electrically stimulating the ablated arteries. RNS can also increase serum noradrenaline and adrenaline concentrations before RDN, while these elevations were attenuated after RDN. Furthermore, Chinushi et al. [22] demonstrated that the attenuation of BP elevation induced by RNS was related to the severity of histological injury. The increase in RNS-induced BP was nearly completely inhibited following 20 or 25 W ablation, and obvious tissue injury to the renal nerves was observed. When the radiofrequency current was delivered at 15 W, the increase in RNS-induced BP was markedly attenuated, and only minor histological changes of the renal artery could be observed. RNS was used to guide RDN by Lu et al. [23] in 2015. Thirteen Chinese Kunming dogs with naturally high BP were included. RNS was applied to map afferent sensory nerves, and radiofrequency energy (8–15 W) was delivered at the sites where RNS could induce a BP elevation of more than 10 mmHg. At 3 months, a marked BP reduction

of 24.4/10.7 mmHg was observed in the RDN group. The RDN group also showed significant decreases in serum noradrenaline concentrations, with reductions of 0.86 nmol/L. Meanwhile, a slight BP reduction and no significant serum noradrenaline changes were observed in the control group.

Gal et al. performed one of the first several clinical studies [24], and the results illustrated the feasibility of renal sympathetic denervation (RSD) guided by RNS in patients. First, RNS was applied at the renal arteries, and then a standard ablative procedure was performed, followed by repeated RNS at the same site with a maximum BP increase. The average SBP increased by 43 mmHg during RNS, while the SBP only increased by 9 mmHg after RDN (⩽8 W). This result proved the initial evidence that RNS can produce an acute and transient increase in BP, and this reaction was blunted after RDN. The same group of investigators [25] further correlated a relationship between the acute BP increase response to RNS before and after RDN (≤8 W) with BP changes at 3–6 months. BP changes in responses to RNS were monitored before and immediately after RDN. Ambulatory BP was evaluated at 3–6 months. Consistent with previous studies, the immediate BP elevation induced by RNS was attenuated after RDN (SBP increased by 50 mmHg before RDN and only 13 mmHg after RDN). The ambulatory SBP was 137 mmHg at a median follow-up of 4.5 months, while the baseline was 153 mmHg. RNS-induced maximum BP elevation before RDN was correlated with the drop of 24 h ambulatory BP after RDN at 6 months. Interestingly, RNS-induced BP elevation before versus immediately after RDN was closely correlated with long-term BP reduction. Since the radiofrequency current can also induce an increase in BP during the RDN procedure [21, 23], Xu et al. [26] confirmed that the increased BP during radiofrequency current ablation can also serve as an index to predict BP reduction after the RDN procedure. These studies initially demonstrated the safety and feasibility of RNS-guided RDN, and the blunted response of RNS-induced BP elevation after RDN can be used as an acute endpoint to evaluate the efficacy of RDN and predict long-term BP response.

There is a critical unmet clinical need to find simple and reproducible indexes for successful denervation before, during and immediately after the RDN procedure. These indexes should provide direct feedback to RDN performers and can guide the procedure operators to identify sympatho-stimulatory nerve-enriched sites and avoid sympathetic inhibitory sites. Barber-Chamoux and Esler reported that finding an acute predictor of renal nerve damage is critical to ensure the success of renal denervation, and RNS might be the most promising technique [27]. The 2nd European Clinical Consensus Conference for device-based therapies for hypertension [28] also listed that RNS-induced BP changes before and after RDN, and the veno-arterial norepinephrine gradient immediately after RDN can potentially be used to assess the efficiency of RDN. Compared with plasma biomarkers, RNS seems more convenient and easier to use. RNS was used to evaluate the efficacy of RDN and guide denervation in previous clinical studies. Importantly, a study by Lu in a dog model used RNS as a tool not only to guide RDN but also to locate renal nerves with histological evidence [23]. Currently, two clinical trials (SMART study NCT03288142 and CONFIDENT study NCT02777216) in which RNS is being used to guide RDN to treat hypertension are ongoing. The results of these studies are expected.

The roles of renal efferent, afferent nerves, and vagal nerves in responses of BP to renal stimulation

RNS-guided RDN has achieved preliminary success, but the mechanisms related to BP in response to RNS are not yet fully clarified. The sympathetic nervous system plays a significant role in the pathogenesis of hypertension. Renal efferent sympathetic nerves and afferent sensory nerves surround the renal artery in a net-like fashion [29]. The two types of nerves cooperate with each other and participate in the regulation of BP. Stimulating efferent nerves results in a series of physiological events: increased sympathetic activity of kidney and renal vascular resistance, decreased renal blood flow, an activated renin–angiotensin system (RAS), an increased renin secretion rate, increased sodium and water reabsorption, and finally elevation of BP. Renal afferent nerves transmit signals to the central nervous system (CNS). By stimulating afferent nerves, rostral ventrolateral medulla neurons in the brain can be activated, and sympathetic outflow to the whole body would be altered as a result. Accordingly, effective ablation of either efferent or afferent nerves could reduce BP by suppressing sympathetic signals from or to the kidney. Destroying efferent nerve fibers can decrease BP by directly inhibiting renal sympathetic activity, and destroying afferent nerves can inhibit systemic and renal sympathetic activity by interfering with the transmission between the central sympathetic nervous system and kidney. BP elevation mainly started during the initial 10–30 s after RNS and remained within 60–120 s after its cessation [23]. Considering that the immediate effects of activating efferent nerves are mainly limited to the kidney, it would take more time to stimulate efferent nerves to raise the BP. However, the activation of afferent nerves can immediately mediate systemic sympathetic nervous activity. Thus, the immediate systemic BP response evoked by RNS was proposed as an afferent response (Fig. 2).

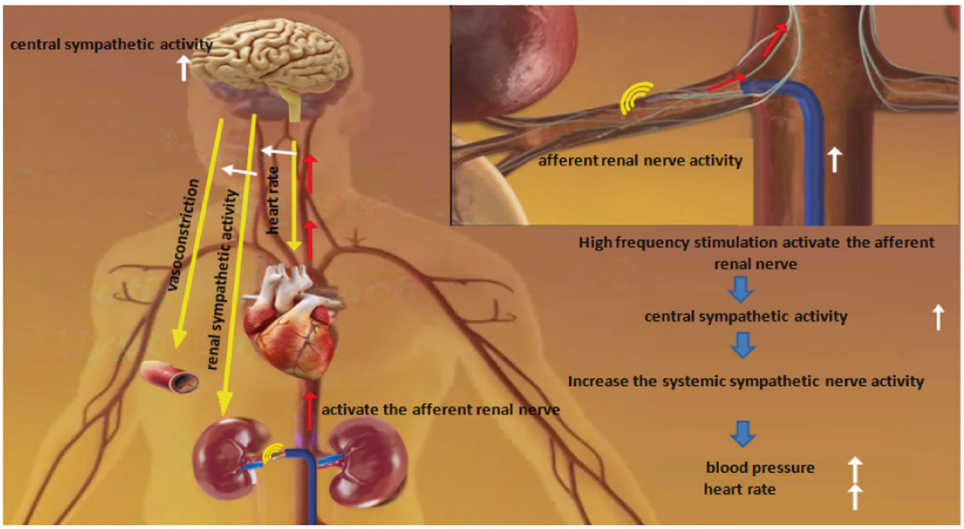

Fig. 2 The mechanisms related to the BP response to RNS

A study by Fujisawa et al. [30] showed that excessive activation of renal afferent nerves can induce BP elevation. However, when CV-11974 (an angiotensin II receptor blocker) was injected into the intracerebroventricular region of the rats, the vasopressor response was suppressed. Similar to injection of CV-11974, surgical renal denervation could also suppress the sympathoexcitatory effects. Experimental and clinical evidence confirmed that renal afferent nerves contributed to autonomic and hemodynamic systems by regulating the RAS pathway of the CNS.

Anatomical analysis of peri-arterial renal nerves in humans have indicated that efferent and afferent nerves are distributed within or around the renal artery wall, and the efferent nerves have predominance [31, 32]. More importantly, efferent nerves run parallel with afferent nerves, even in the same nervous bundle. Based on this anatomical and histological structure, RNS can not only directly map afferent nerves but also map the efferent nerves, and the integrated physiological responses such as changes in BP are due to electronic stimulation, depending upon which nerves are dominant in the bundle. Therefore, it is feasible for RNS-guided RDN to accurately damage efferent and afferent nerves at the same time.

Lu et al. [23] showed that no significant BP elevation was induced by RNS at the distal portion of the renal artery. Similarly, Chinushi et al. [21] showed that BP elevation can only be induced at the proximal segment of the renal artery. Anatomy of the renal nerves also showed that the prevalence of afferent nerves decreases from the proximal to distal aspect [31]. Henegar et al. [33] further indicated that denervating different regions of the renal artery produced different degrees of renal norepinephrine decrease in pigs. Norepinephrine levels were reduced by 12%, 45%, and 74% when denervation was performed at the ostium, near the bifurcation of the main artery, and in branches of the renal artery closer to the kidney, respectively. This result indicated that more efferent nerves were located at the distal portion of the artery. Since efferent nerves cannot evoke an immediate systemic BP response, we hypothesized that denervation of the sites where the SBP increased <10 mmHg during RNS may also result in BP reduction. This hypothesis needs to be further proven.

In addition to the presence of efferent and afferent nerves, the existence of vagal nerves around renal arteries was demonstrated in animal models years ago. However, this concept was arguable over the years because of the anatomical differences between animals and humans. The existence of vagal fibers in humans was demonstrated in 2015 by using nitric oxide synthase (NOS) as a specific marker [32]. Vagal fibers contribute ~8.7% to the total cross-sectional nerve area and exist closer to the lumen than do efferent or afferent nerves. The role of the vagal nerves on renal physiology was not clarified, and it is debatable whether these nerve fibers are defined as vagal. Fudim believed that it is better to define these nerves as sympathetic inhibitory fibers [1]. In theory, electrical stimulation of vagal nerves would cause an acute BP reduction. If only these vagal or sympathetic inhibitory fibers are destroyed, an imbalance will be induced between sympathetic and parasympathetic nerves, resulting in sympathetic dominance. This may explain the elevated BP in some patients after the RDN procedure. Murai et al. [34] indeed observed a clinical case in which BP decreased from 140/80 to 100/68 mmHg in response to RNS. A study by De Jong et al. [2] included 35 patients, and RNS was performed under general anesthesia before and immediately after RDN. In response to electrical stimulation, 62% of sites caused SBP to increase by more than 10 mmHg, 30% of sites caused SBP to increase by ≤10 mmHg, and 4.5% of sites caused an up to 8 mmHg reduction in SBP. It is believed that the

RNS-induced BP decrease was observed when the vagal nerves were located in close proximity to the artery wall and were captured by RNS. Thus, RNS is promising for identifying sympathetic and vagal nerves or sympathetic inhibitory nerves around renal arteries and for preventing inadvertent ablation of vagal nerves. The distribution of vagal nerves was not provided in this study. We utilized NOS and calcitonin gene-related peptide as immunohistochemical markers to stain vagal and afferent renal nerves in a canine model, and our results are shown in Fig. 3 (unpublished observations): vagal and afferent renal fibers co-exist in the same bundle. As we have discussed previously, the same bundle may contain three different types of nerve fibers: efferent, afferent, and vagal nerves; the acute increase and long-term decrease in BP occur in response to stimulating and ablating the bundle, respectively, which is an integrated physiological event that depends upon which nerve fibers are dominant at this particular site. If a vagal dominant site is futilely denervated, it may partly neutralize the BP drop caused by sympathetic denervation or even augment the BP. Thus, we propose that the net effects of RDN on BP involve the rebalance between the sympathetic and parasympathetic systems due to the procedure.

Preclinical research of different BP response patterns to RNS

It is important to identify BP change patterns during RNS and determine which site should be ablated and avoid futile ablation. Thus, we performed a study to explore the relationship between the phenotype of renal nerves and BP responses during RNS, and the study included 24 healthy adult Chinese Kunming dogs with naturally high BP

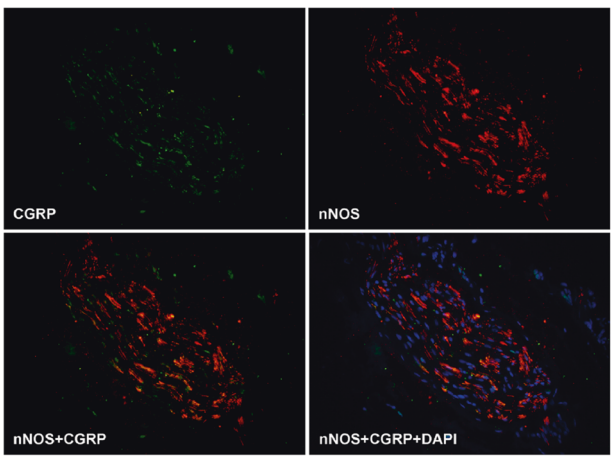

Fig. 3 Renal nerve images of immunofluorescence. Red channel = nitric oxide synthase (NOS); green channel = calcitonin gene related peptide (CGRP)

(unpublished observations). All dogs underwent RNS from the distal to the proximal segments of the renal arteries by the bipolar electrodes of the AquaSense catheter (Synaptic Medical Ltd., Beijing, China). Invasive BP changes during RNS were recorded. Owing to heterogeneous fibers existence, we observed at least five types of BP responses during RNS (Fig. 4):

Type 1, BP was elevated persistently during RNS with or without heart rate increases.

Type 2, BP dropped at the beginning of the stimulation and then increased and exceeded the baseline level.

Type 3, BP dropped at the beginning and then increased but never exceeded the baseline level.

Type 4, BP was unchanged during RNS.

Type 5, BP dropped persistently during RNS.

The type 1 BP response often occurred after 10 s of renal electrical stimulation. This result indicates that the afferent renal nerve is dominant and located right between two electrodes, which are used to deliver the stimulated current, and could be captured persistently. Therefore, electrical stimulation signals are transmitted to the CNS and increase central sympathetic activity, leading to an increasing central sympathetic output to the entire body. It causes a series of physiological effects, including peripheral vasoconstriction and increases in myocardial contractility and cardiac output, leading to BP elevation. If the afferent and efferent nerves are in parallel, even in the same bundle, the efferent renal nerves could be captured by electrical stimulation and manifested as renal artery contraction. The efferent sympathetic signaling to kidneys is responsible for the elevation of BP by increasing renal vascular resistance, by the release of renin from juxtaglomerular cells and by increasing tubular sodium and water reabsorption. We strongly suggest ablating these sites. The type 2 BP response represents simultaneous activation of sympathetic afferent and vagal afferent nerves. Because the transmitted speed of vagal fibers to the CNS is faster than that of afferent nerves, the BP first decreases and then gradually increases. The net effect is BP elevation. The impacts of sympathetic afferent nerves on BP are more dominant than those of vagal fibers. Therefore, our recommendation is to ablate these sites. The type 3 BP response also indicates that sympathetic afferent and vagal afferent nerves are activated simultaneously. Ultimately, the integrated effects of these two types of nerves maintain the BP at the baseline level, representing a balanced interaction between the function of the two renal nerves. Therefore, such sites should not be ablated. The type 4 BP response represents a state in which there is no renal nerve or nonsympathetic/nonparasympathetic nerve present in the range of the two electrodes. Since the BP was not changed, this site plays a minor role in BP regulation and, therefore, should not be ablated. The type 5 BP response represents a site with predominant vagal sensory

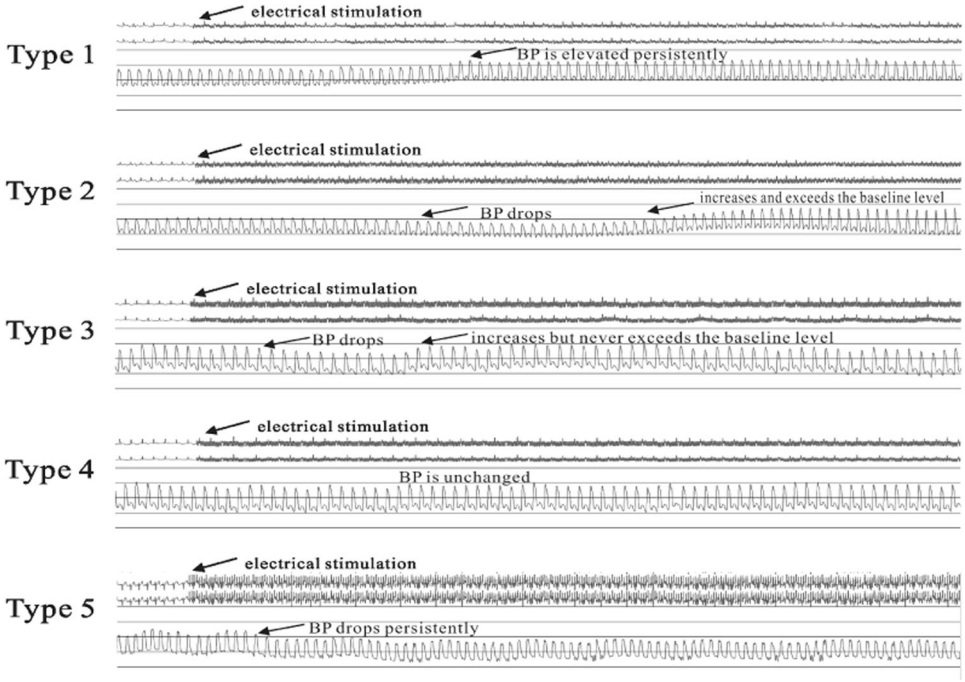

Fig. 4 The different types of BP patterns in response to electrical stimulation

afferent fibers. Considering that ablation at such sites may lead to reduced vagal nerve activity and promotion of sympathetic nerve activity, ablation should be prohibited at such sites.

Compared with global RDN, selective RDN has advantages in identifying "good denervation" [1]. The significant heterogeneity of the clinical response to global RDN has seriously affected the progress of the therapy. Since RNS may guide selective ablation, targeted RDN might result in better BP lowering effects. RDN as a treatment option for hypertension has strong scientific and clinical rationales, and improving the efficacy and ensuring the safety of RDN are difficult challenges. Recent experimental and clinical studies have provided initial evidence that RNS might be utilized to map and identify nerve types around renal arteries, such as sympathetic stimulatory, parasympathetic, or sympathetic inhibitory nerves, by analyzing BP response patterns to RNS and determining sites to ablate or not ablate. The efficacy and safety of RDN might also be improved by RNS-guided RDN, respectively, because net effects of selective RDN on BP reduction can be greater than global RDN and fewer ablations are needed when using this approach. More preclinical studies and large-scale randomized, blinded, and sham-controlled clinical studies are warranted to explore the detailed mechanisms of RNS-guided RDN and its values in clinical practice.

Type 1, BP was elevated persistently during RNS with or without heart rate increases.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest. YHY is a consultant to SyMap Medical Ltd. JW is a cofounder of SyMap Medical Ltd.

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