The role of renal nerve stimulation in percutaneous renal denervation for hypertension: A mini-review

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Abstract
Recent trials have demonstrated the efficacy and safety of percutaneous renal sympathetic denervation (RDN) for blood pressure (BP)-lowering in patients with uncontrolled hypertension. Nevertheless, major challenges exist, such as the wide variation of BP-lowering responses following RDN (from strong response to no response) and lack of feasible and reproducible peri-procedural predictors for patient response. Both animal and human studies have demonstrated different patterns of BP responses following renal nerve stimulation (RNS), possibly related to varied regional proportions of sympathetic and parasympathetic nerve tissues along the renal arteries. Animal studies of RNS have shown that rapid electrical stimulation of the renal arteries caused...
renal artery vasoconstriction and increased norepinephrine secretion with a concomitant increase in BP, and the responses were attenuated after RDN. Moreover, selective RDN at sites with strong RNS-induced BP increases led to a more efficient BP-lowering effect. In human, when RNS was performed before and after RDN, blunted changes in RNS-induced BP responses were noted after RDN. The systolic BP response induced by RNS before RDN and blunted systolic BP response to RNS after RDN, at the site with maximal RNS-induced systolic BP response before RDN, both correlated with the 24-h ambulatory BP reductions 3–12 months following RDN. In summary, RNS-induced BP changes, before and after RDN, could be used to assess the immediate effect of RDN and predict BP reductions months following RDN. More comprehensive, large-scale and long term trials are needed to verify these findings.

**KEYWORDS**
hypertension, percutaneous renal sympathetic denervation, renal nerve stimulation

1  |  INTRODUCTION

Increased sympathetic nerve activity leads to the occurrence and progression of hypertension. Renal efferent nerve hyperactivity increases sodium reabsorption and activates the renin-angiotensin-aldosterone system. Percutaneous renal sympathetic denervation (RDN) can be used to disrupt renal afferent and efferent sympathetic nerves and is a rational technique to modulate central sympathetic outflow and renal physiology and achieve sustained BP reductions.

As early as 2009, the first case of catheter-based radiofrequency RDN was reported, which showed a substantial and sustained reduction in BP. Thereafter, the SYMPLICITY HTN-1 and 2 trials were conducted and demonstrated the persistent BP reduction and good safety of RDN. However, this result was not replicated in the following blinded sham-controlled Simplicity HTN-3 trial where 535 patients with uncontrolled treatment-resistant hypertension were randomized to RDN or a sham procedure. The study failed to show a significant ambulatory BP reduction difference between the two arms. This discrepancy in the results incited fervent discussion, and many possible explanations were put forward, such as procedural variations, change of medication use, physician inexperience, or patient non-adherence.

After carefully considering the weaknesses and limitations of the SYMPLICITY HTN-3 trial, several well-designed, second-generation randomized sham-controlled RDN trials (DENERHTN trial, SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, RADIANCE-HTN SOLO, and RADIANCE-HTN TRIO) were conducted and consistently demonstrated clinically meaningful BP reductions, without serious adverse events. As a result, the consensus statement of the Asia Renal Denervation Consortium suggested RDN could serve as an initial therapy for hypertension control, either alone or in combination with antihypertensive medications.

The wide spectrum of BP-lowering responses following RDN, from strong response to no response, and lack of a feasible and reproducible peri-procedural predictor to indicate a good BP-lowering response are major challenges to the application of RDN. In light of this, renal nerve stimulation (RNS) is proposed as a promising method to test the immediate effect of RDN. This review summarizes the published data on the use of RNS with RDN.

2  |  PATHOPHYSIOLOGICAL MECHANISMS

2.1  |  Pathophysiological mechanisms of RNS

Renal nerves consist of afferent sensory, efferent sympathetic, and parasympathetic fibers and are distributed unequally along renal arteries. Activation of afferent renal nerves may cause BP elevation by increasing central sympathetic nerve activity and elevating plasma norepinephrine spillover. Renal efferent sympathetic nerve overactivity modulates tubular sodium reabsorption, renal blood flow, and renin release, which all cause BP elevations. RNS can lead to increase, decrease, or no changes in BP. The physiological responses of these nerve fibers to RNS depend on the overall responses of the stimulated fibers. Nevertheless, the complete pathophysiological mechanisms of RNS are not fully understood yet. Stimulation of renal efferent nerves potentially increases arterial pressures secondary to the increased renin secretion, tubular sodium reabsorption, and renal vascular resistance. RNS-induced increased renin release occurred 10 min after RNS in anesthetized dogs. Hoogerwaard and colleagues suggested that RNS-induced BP changes could be caused by an increased central sympathetic tone via the sympato-excitatory renal afferent reflex. This is because the RNS-induced BP change was observed soon (within 3 min) after RNS. In our experience, RNS consistently elicited increases in BP, which generally peaked within 2 minutes after discontinuation of 1-min RNS. In the first half of 1-min RNS period, transient decrease in BP may occur, which then universally turns into increase in BP (unpublished data).
2.2 Pathophysiological mechanisms of renal denervation

The exact mechanisms by which RDN causes long-term BP lowering have not yet been fully elucidated but are likely to include reduced renal afferent and efferent sympathetic activity and effects on the renin-angiotensin system. Disruption of renal afferent nerves may modulate central sympathetic outflow to achieve the goal of BP reduction. Destruction of efferent sympathetic nerves can result in a decreased plasma renin activity, a significant reduction of water and sodium reabsorption and also inhibition of renal renin-angiotensin system overactivation. However, previous studies showed inconsistent results regarding changes in plasma renin activity following RDN.22–24 A possible confounder is the prescribed antihypertensive medications in these studies that may affect renin and aldosterone levels. The SPYRAL HTN-OFF MED Pivotal trial demonstrated that RDN therapy significantly reduced plasma renin activity 3 months following RDN in drug-naive hypertensive patients.25 Further, RDN in patients with higher levels of plasma renin activity at baseline was associated with a significantly greater reduction in office and 24-hour systolic BP.25 This study provided evidence that RDN may stabilize the renin-angiotensin-aldosterone system by disrupting renal efferent nerve hyperactivity. Plasma renin activity is positively associated with higher resting heart rate, and high-renin hypertension is often associated with higher heart rates.26 RDN usually causes heart rate reduction in post-RDN follow-up.

Of note, animal studies have demonstrated the occurrence of renal re-innervation. Originally, renal nerve re-innervation and the recovery responses to electrical stimulation were reported 11 months after RDN in normotensive sheep.27,28 The subsequent study demonstrated a sustained reduction in BP and reduced anatomical and functional renal nerve re-innervation 30 months after RDN in hypertensive sheep.29 The mechanism of sustained BP-lowering response from RDN in human studies is ambiguous. The function and extent of re-innervation following RDN in human need further studies to clarify.

3 RENAL NERVE STIMULATION STUDIES

3.1 Renal nerve stimulation in animal studies

The first RNS animal study reported by Chinushi and colleagues showed that rapid electrical stimulation at the proximal portion of the renal arterial wall in anesthetized dogs increased BP and heart rate (HR) before RDN and that the rise in BP and HR were attenuated when the ablated renal artery was stimulated.30 Before RDN, BP was significantly elevated from 145 ± 15/85 ± 13 mmHg to 189 ± 21/111 ± 19 mmHg, and HR increased from 116 ± 9 per minute to 130 ± 6 per minute. After RDN, no significant changes in BP (from 150 ± 20/90 ± 16 mmHg to 152 ± 20/92 ± 17 mmHg) or HR (from 124 ± 14 per minute to 124 ± 14 per minute) were noted. The serum epinephrine and norepinephrine concentrations were significantly elevated after RNS before RDN and became blunted after RDN. Furthermore, in a study by Sun and colleagues in which the renal artery nerves of 16 anesthetized dogs were electrically stimulated, there was a significant rise in BP after RNS, whereas the change in HR was nonsignificant.31 The authors proposed baroreceptor-independent sympathetic activation as the possible pathophysiological mechanism to explain the observed differential BP and HR responses.32 Lu and colleagues performed selective RDN on RNS-responsive proximal renal arteries (systolic BP increased ≥10 mmHg after RNS) and achieved sustained BP reduction and sympathetically induced hypertensive in a canine model. Conversely, the control group showed unchanged BP and plasma norepinephrine concentrations.33 In addition, no significant HR response was noted during RNS to the proximal BP-responsive renal arteries.

In order to delineate the spectrum of BP and HR changes from RNS, Zhou and colleagues conducted RNS in 483 stimulation sites in 24 anesthetized Kunming dogs. Five different BP change patterns and no significant HR response were noted. The authors hypothesized that the variation in BP change was attributed to variability in the proportion of excited sympathetic-excitatory fibers and sympathetic-inhibitory fibers.19

In an RNS study conducted by Liu and colleagues, they randomly assigned 21 dogs into three groups: a strong-response sites ablation group, a weak-response sites ablation group, and an RNS-control group. They found that selective RDN at sites with strong RNS-induced systolic BP response led to a more efficient BP-lowering effect 4 weeks following RDN than ablation at the weak-response sites and that in the control group.34 Blunted systolic BP response to RNS after RDN was also associated with a more efficient BP-lowering effect. They concluded that RNS was effective in identifying the nerve-rich area and optimizing the RDN procedure. Another study by Qian and colleagues demonstrated that trans-vascular high-frequency aorticorenal ganglia (ARG) pacing was a feasible method for localizing the ARG and inducing renal arterial vasoconstriction and concomitant BP elevation. They suggested that abolition of ARG pacing-induced renal arterial vasoconstriction may serve as a physiological endpoint for RDN.35

In summary, RNS in animal models demonstrated an immediate BP response soon after stimulating renal nerves, which may reflect the cumulative effects of excited sympathetic fibers and parasympathetic fibers. The RNS-induced responses would be blunted after sufficient ablation at the renal artery sites.34 Ablation at sites with enhanced systolic BP responses to RNS and blunted BP response to RNS after RDN were both associated with a greater BP-lowering effect following RDN (Table 1).

3.2 Renal nerve stimulation results from human studies

In 2015, the first reported RNS study in anesthetized humans conducted by Gal and colleagues demonstrated that RNS caused a temporary increase in BP. Eight people with resistant hypertension were included for RDN. RNS was performed 1 min before and after RDN. In the study, the pre-RDN systolic BP change induced by RNS was 43±15
| Study               | Sample size | Sedation                  | Stimulation protocol                                      | Stimulation sites                                      | RNS responses before RDN                        | RNS responses after RDN                         | BP changes following RDN |
|---------------------|-------------|---------------------------|----------------------------------------------------------|--------------------------------------------------------|------------------------------------------------|------------------------------------------------|--------------------------|
| Chinushi et al (2013) [30] | 8 dogs      | sodium thiamylal and pentazocine (1 mg/kg) | Frequency: 20 Hz, Pulse width: 5 ms, Output: 15 mA, Duration: 30 s | Right and left proximal renal arteries                  | Before RDN, RNS increased BP from 150 ± 16/92 ± 15 to 173 ± 21/105 ± 16 mmHg, RNS increased HR from 119 ± 9 bpm to 131 ± 7 bpm. Significant increase in BP and HR before RDN | After RDN, the RNS induced BP change from 150 ± 20/90 ± 16 mmHg to 152 ± 20/92 ± 17 mmHg and the HR change from 124 ± 14 bpm to 124 ± 14 bpm. BP and HR changes were attenuated after RDN | NA |
| Sun et al (2015) [31] | 16 dogs     | 3% sodium pentobarbital    | Frequency: 20 Hz, Pulse width: 1 ms, Output: 12 mA, Duration: NA | Right and left proximal renal arteries                  | Before RDN, RNS increased BP from 134 ± 24/96 ± 18 to 157 ± 26/114 ± 18 mmHg. Significant increase in BP, but no effect on HR | NA                                              | NA                       |
| Lu et al (2015) [33] | 13 dogs     | 3% sodium pentobarbital    | Frequency: 20 Hz, Pulse width: 2 ms, Output: 8 mA, Duration: up to 60 s | Right and left proximal to distal renal arteries         | Significant increase in BP in the RNS-responsive group. BP changes were 6.0 ± 5.0/3.4 ± 5.5, 16.9 ± 11.7/11.2 ± 8.5, and 17.1 ± 8.4/8.5 ± 5.3 mmHg in 20 s, 40 s and 60 s. No significant effect on HR. | Attenuated increase in BP: 1.3 ± 3.0/1.0 ± 2.5, .8 ± 3.9/1.5 ± 3.4, and 1.5 ± 4.5/1.7 ± 3.8 mmHg in 20 s, 40 s and 60 s. | At 3 months, BP significantly reduced in the proximal RDN group with reductions of 24 ± 13/11 ± 10 mmHg. |
| Zhou et al (2021) [39] | 24 Chinese Kunming dog | 3% sodium pentobarbital | Frequency: 10 Hz, Pulse width: 2 ms, Output: 12 mA, Duration: 60 s | Right and left renal artery, from bifurcation to ostium | Five different patterns of BP responses to RNS in 483 stimulated sites: (1) continuous ascending (26.9%), (2) declining and then rising over baseline (11.8%), (3) declining and then rising but below baseline (14.5%), (4) fluctuating in the vicinity of baseline (39.5%), and (5) continuous declining and finally keeping steady below baseline (7.2%). There were no effects on HR. | NA                                              | NA                       |
| Liu et al (2019) [34] | 21 dogs into 3 groups: SRA group, WRA group, and control group | 3% sodium pentobarbital | Frequency: 20 Hz, Pulse width: 2 ms, Output: 15 mA, Duration: 60 s | Right and left proximal to distal renal arteries         | In the SRA group, RNS increased BP from 181 ± 17/113 ± 12 to 202 ± 16/122 ± 14 mmHg (p = .002), while in the WRA group, RNS increased BP from 194 ± 19/123 ± 27 to 199 ± 18/126 ± 28 mmHg (p = .030) | In the SRA group, BP increased from 184 ± 15/116 ± 11 to 191 ± 16/119 ± 12 mmHg, while in the WRA group, BP increased from 194 ± 17/122 ± 29 to 198 ± 16/126 ± 29 mmHg. The RNS-induced SBP-elevation was significantly blunted in the SRA group (8 ± 5 versus 21 ± 7 mmHg, p = .001). | 4 weeks after RDN, the reduction of SBP in the SRA group was greater than that in the WRA group and control group. (29 ± 7 vs. 15 ± 6 vs. 4 ± 7 mmHg, p = .002) |

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; RDN, renal denervation; RNS, renal nerve stimulation, SBP, systolic blood pressure; SRA, strong response area; WRA, weak response area.
| Study                              | Sample size | Anesthesia                                      | Stimulation protocol                                      | Stimulation sites                                      | RNS responses before RDN                                   | RNS responses after RDN                                    | BP changes following RDN                           |
|-----------------------------------|-------------|-------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| Gal et al. (2015)                 | 8           | Propofol (2–4 mg/kg/min)                        | Frequency: 20 Hz, Pulse width: 2 ms, Output: 5, 10, 15, 20 mA, Duration: 1 min | Right and left proximal renal arteries                     | Significant increase in BP from 108/55 to 132/68 mmHg ($p = .001$) | Maximum SBP response was significantly blunted (43 vs. 9 mmHg, $p = .002$) | NA                                                       |
| de Jong and colleagues (2018)     | 35          | Induced by Propofol and maintained by Fentanyl | Frequency: 20 Hz, Pulse width: 2 ms, Output: 20 mA, Duration: 1 min or less if SBP > 180 mmHg | Right and left proximal to distal renal arteries                  | 289 RNS sites in 35 patients, 180 sites (62%) showed a positive BP response (increase in SBP > 10 mmHg), 86 sites (30%) an indifferent response, 13 sites (4.5%) showed a decrease in SBP up to 8 mmHg. | NA                                                        | NA                                                       |
| de Jong and colleagues (2016)     | 14          | Induced by Propofol and maintained by Fentanyl | Frequency: 20 Hz, Pulse width: 2 ms, Output: 20 mA, Duration: 1 min or less if SBP > 180 mmHg | At four sites in each renal arteries                      | A maximal SBP increase of 50±27 mmHg                     | An SBP increase of 13±16 mmHg at the site with the maximal SBP increase before RDN | 24-hour systolic BP was 153±11 mmHg before RDN and decreased to 137±10 mmHg at 3–6-month follow-up. RNS-induced BP changes before versus after RDN were correlated with changes in 24-h ABPM 3 to 6 months after RDN. |
| de Jong and colleagues (2016)     | 21, 9 patients had accessory renal artery | Induced by Propofol and maintained by Fentanyl | Frequency: 20 Hz, Pulse width: 3 ms, Output: 20 mA, Duration: 1 min or less if SBP > 180 mmHg | At four sites in both right and left renal arteries; at ostium of accessory renal artery | RNS elicited an increase in SBP, both in main (26±3 mmHg) and accessory (24±7 mmHg; $p = .047$) renal arteries. | RNS-induced SBP increase was blunted in the main renal arteries ($\Delta$SBP, 9±4 mmHg; $p = .020$) but not in the non-denervated accessory renal arteries ($\Delta$SBP, 27±8 mmHg; $p = .917$) | NA                                                       |
| Hoogerwaard and colleagues (2021) | 44          | Induced by Propofol                             | Frequency: 20 Hz, Pulse width: 2 ms, Output: 20 mA, Duration: 1 min or less if SBP > 180 mmHg | A minimum of 4 sites in each renal arteries                | The RNS-induced maximal systolic BP rise was 43±21 mmHg. | The RNS-induced systolic BP change at the site with the maximal systolic BP increase before RDN decreased to 9±12 mmHg. | Mean 24-h systolic/diastolic BP decreased from 147±12/82±11 mmHg at baseline to 135±11/76±10 mmHg at 6–12 months follow-up. RNS-induced BP changes before versus after RDN were correlated with changes in 24-hour ABPM 6 to 12 months after RDN. |

**Abbreviations:** ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; RDN, renal denervation; RNS, renal nerve stimulation; SBP, systolic blood pressure
mmHg, and the post-RDN systolic BP change significantly declined to 26±10 mmHg (p = .0002).36

In order to delineate the response of RNS, de Jong and colleagues enrolled 35 patients with drug-resistant hypertension for RDN. Intravenous anesthesia was implemented throughout the course. Of the 289 sites of renal artery stimulation, 62% had a sympathetic response with a systolic BP increase of >10 mmHg; 30% had an indifferent response to RNS, while the remaining had a vagal response with a drop in BP and bradycardia.20 The study provided evidence of the potential benefit of RNS in identifying relative distribution of sympathetic and parasympathetic nerve fibers along the renal arteries and guiding selective ablation in RDN. The same research group also evaluated the correlation between the changes in RNS-induced BP increase before and after RDN. The same research group also demonstrated that evaluation in main renal arteries, RNS-induced systolic BP increase was 50±27 mmHg; after RDN, the RNS-induced systolic BP change was attenuated to 13±16 mmHg (p < .001). At 3 to 6 months post-RDN, the ambulatory BP significantly declined to 137±10/80±9 mmHg (p = .003). RNS-induced maximum systolic BP increase before RDN and RNS-induced BP changes before versus after RDN were both correlated with changes in 24-h ABPM 3 to 6 months after RDN. The study suggested the benefit of RNS as a tool for assessment of the efficacy of RDN and prediction of the BP response to RDN. The same research group also demonstrated that RNS in both main and accessory renal arteries elicited a substantial systolic BP increase (26±3 mmHg, p < .001 in a main renal artery and 24.3±7.4 mmHg, p = .047 in an accessory renal artery). After renal denervation in main renal arteries, RNS-induced systolic BP increase was blunted in the main renal arteries (systolic BP change, 9±4 mmHg, p = .02), but not in the non-denervated accessory renal arteries (systolic BP change, 27±8 mmHg, p = .917).38 The authors demonstrated that an increase in BP can be elicited in an accessory renal artery, and the non-responsiveness to RDN might be due to anatomical variations in the renal arteries and incomplete ablations. In 2021, a study done by Hoogerwaard and colleagues which enrolled 44 patients with resistant hypertension in a single-center RNS trial, was reported. Before RDN, the RNS-induced systolic BP rise was 43±21 mmHg, and decreased to 9±12 mmHg after RDN. The RNS-induced systolic BP response after RDN varied from –9 to 45 mmHg. The mean 24-h systolic/diastolic BP decreased from 147±12/82±11 mmHg at baseline to 135±11/76±10 mmHg at 6–12 months follow-up (both p < .001). Among the 36 patients with available records of acute RNS-induced BP changes, 6 (17%) patients with <0 mmHg residual RNS-induced BP response after RDN, at the site with the greatest systolic BP response before RDN, had a significantly lower mean 24-h systolic BP at follow-up (Table 2).39

These studies supported the use of RNS as a periprocedural tool to guide RDN and assess its immediate effect. A small RNS-induced systolic BP increase after RDN may be a good predictor of the BP-lowering effect of RDN. Conversely, persistent BP increase induced by RNS immediately after RDN may indicate insufficient or incomplete ablation. Large comprehensive RNS studies are needed to verify these results.

### 4 CONCLUSIONS

The BP reduction response by RDN arises from the interruption of both renal afferent and efferent sympathetic nerves-mediated neurohormonal pathways. Further research is needed to resolve the issues of variation in RDN responses and lack of a feasible and reproducible peri-procedural indicator for RDN. Preliminary studies in animals and humans have shown that RNS-induced BP changes, before and after RDN, could serve as a useful tool in assessing the immediate effect of RDN and predicting BP reductions months following RDN.

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### CONFLICTS OF INTEREST

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