Sensing Renal Nerve Activities Before, During and After Denervation: SyMap

Jie Wang[1,2,3*], MD, PhD, Yue-Hui Yin[4], MD, Yue Wang[2,3], MS, Wei Ma[5], MD, Weijie Chen[4], PhD

1. Division of Cardiology, Department of Medicine, College of Physicians & Surgeons, Columbia University, NY, USA
2. Academy of Clinical and Translational Research, Jiangsu Province Hospital, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China
3. SyMap Medical (Suzhou), Ltd., China
4. Department of Cardiology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
5. Department of Cardiology, Peking University First Hospital, Beijing, China

*** Correspondence:**
Dr. Jie Wang, Email: jw147@columbia.edu, jay329329@yahoo.com
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Abstract

The safety and efficacy of renal denervation (RDN) for the treatment of hypertension have been repeatedly confirmed by a number of studies. However, an approximately 30% non-responder rate was consistently observed among various energies-based RDN. This phenomenon might result from non-selective, global RDN as different nerve types are innervated around the renal artery and futile, even wrong, ablations of non-sympathetic nerves could cause detrimental effects. Thus, a readout for mapping renal nerves and selective sympathetic denervation before, during and after RDN is an urgent/unmet clinical need for this therapy. Results of recent studies demonstrated solid anatomy, physiology and histology evidences to support renal electronic stimulation as a tool for renal mapping and selective denervation. Using renal stimulation, we should be able to identify proper sites for RDN, monitor the effects of RDN and confirm an effective RDN before, during and after the procedure, respectively. With a newly developed renal mapping/selective denervation system, we are conducting a pivotal trial to test the safety and efficacy of selective renal sympathetic denervation to treat uncontrolled hypertension.

Keywords: Renal denervation, Hypertension, Renal nerve activity, Sympathetic nerves, Renal stimulation, Mapping renal nerves, Selective sympathetic denervation, Renal mapping/ selective system, SyMap, SMART Study

The Achilles Heel of the Field: Lack of Readouts to Indicate Efficient Renal Sympathetic Denervation

The concept of RDN to treat hypertension can be traced back to 1950s, in a large scale of study by Smithwick and Thompson who showed that blood pressure (BP), mortalities and survival rates of hypertensive patients were significantly improved by thoracolumbar splanchnicectomy [1], demonstrating the effectiveness of RDN on hypertension. Because of severe side effects of the surgical RDN and developments of pharmaceutical therapies, the surgical approach to denervate renal nerves was fired from clinical practice. Although sophisticated drug therapies have been available for hypertension, new therapies for the disease are still an unmet clinical need since social and economic burdens of this disease have become more severe in recent years, and the issues of drug compliance and drug resistance are never really addressed. There are 70[2], 150[3], and 245[4] million hypertensive patients in US, EU countries and China, respectively, and the uncontrolled rate is very high. Krum et al. brought a new hope for RDN in 2009, these investigators performed a proof-of-concept study to denervate renal nerves by a dedicated catheter in patients with resistant hypertension and demonstrated that interventional device-based RDN could lead to a significant reduction in BP with excellent safety profiles [5]. Since then, a series of clinical studies have proved the efficacy and safety of RDN to treat hypertension [6-10]. However, Symplicity HTN-3[11], the first double-blinded, randomized, sham controlled trial showed that the BP difference between RDN and sham group was not observed at 6 months. Investigators realized that two major factors interfered with the effects of device-based RDN on

BP and led to the failure of the Symplicity HTN-3 study: poor drug compliance during the trial, and lack of a readout before, during and after RDN to confirm an effective renal sympathetic denervation [12]. Newly initiated Spyral Global Off-Med and On-Med studies after the failure of Symplicity HTN-3 trial partially addressed the issue of drug compliance by both patients who enrolled in the study and did not take any antihypertensive drugs or who followed a restricted drug regimen during the study [6, 9,10]. Both studies further confirmed the efficacy and safety of RDN but the amplitude of office systolic BP reduction was moderate: around 10mmHg, because 20-30% patients were so-called no-responders whose BP was not decreased or even increased after RDN [6, 9,10]. This may counteract BP-lowering effects achieved by RDN. This phenomenon was consistently observed across various energies-based RDN devices reported so far. Per Townsend and Sobotka [13], either radiofrequency ablation or ultrasound ablation had an over-all success rate of about 63%. These approximately 30% non-responder rates were also observed among patients with alcohol-mediated RDN, Mahfoud et al reported that decreases of ≥5 and ≥10 mm Hg in office systolic BP at 6 months were recorded in 70% and 61% of patients, respectively [14]. Townsend and Sobotka believed that the ~30% non-responder rates may reflect either technical failures or suboptimal patient selection given the lack of predictors for BP-lowering success. It becomes apparent that a decreasing non-responder rate is a major issue that needs to be addressed. As Esler pointed out, failure to test an effective renal sympathetic denervation "represents the Achilles heel of the field" [15]. Thus, indicators before, during and after the RDN procedure to predict and confirm a successful sympathetic denervation are an urgent unmet clinical need for this therapy.

Mapping Renal Nerves by Renal Stimulation: Anatomy, Physiology and Histology Evidences

Recent developments based on studies of anatomy, physiology and histology in this field made mapping renal nerves and selective RDN possible. van Amsterdam et al. and Mompeo et al. [16,17] examined neural anatomy structures around renal artery and revealed three nerve types: sympathetic, parasympathetic and afferent nerve components (Figure 1); however, Kuichi et al. had different views about the types of these nerves and named these nerves as "pressor nerves", "depressor nerves" and "neutral nerves" depending upon whether BP was increased, decreased or unchanged in responses to electronic stimulation [12]. We [18-20] and other investigators [21,22] have demonstrated that systemic hemodynamics in particular, BP, was increased, decreased or unchanged once an electronic stimulation was delivered to the renal artery, respectively. The direction of change in BP due to the stimulation depends upon which type of renal nerves was activated. We [18] named the sites which increased BP when stimulated as "hot spots", representing sympathetic dominant innervations, the sites which lowered BP when simulated as "cold spots", representing parasympathetic dominant innervations, and locations along the renal artery which do not show hemodynamic effects when stimulated as "neutral spots," which may present no innervations or well balanced sympathetic and parasympathetic innervations (Figure 2). Mapping sympathetic/pressor nerves or hot spots for selective ablations could expect to cause a significant fall in BP whereas ablations of parasympathetic/depressor nerves or cold spots may result in no effects or even an increase in BP [23, 18], and neutral spots should not be ablated [12]. Results from clinical trials did show that increased BP in some patients after RDN at a 6-month follow-up [6, 9,10] and it may be due to wrong ablations of cold spots. As Tsioufis et al [23] pointed out, renal nerve fibers vary significantly regarding types, numbers and sizes, as well as their distance from the lumen in the proximal and distal segments of renal artery mainstream and branches. Several recent studies [19-25] have illustrated BP responses to renal nerve stimulation in corresponding to the different nerve distributions around renal artery and provided convincing evidences of anatomy,

physiology and histology for the rationales of renal mapping guided by renal nerve stimulation. Regarding the concept of different BP responses to discrete site stimulations, we have demonstrated a substantial reduction in both BP [20, 26] and serum norepinephrine levels in Chinese Kunming dogs, a canine model with a spontaneous high sympathetic tone, after ablating the sites which caused significant rises in BP evoked by renal nerve stimulation, and we confirmed that the BP-lowering effects were proportional to the increases in BP by the stimulation. Histological evidence implied that these sites were innervated by nerve bundles containing sympathetic fibers [19,20] and that the amplitudes of increases in BP to renal stimulation were proportionally determined by the total area and number of renal nerves in stimulated sites (Figure 3). Renal stimulation can be also used to assess whether a successful RDN is achieved. After a successful RDN, BP response to stimulation should be significantly blunted; otherwise, it suggests an inadequate denervation at the target sites and a second ablation on the same site will be needed.

Thus, renal nerve stimulation and changes in BP in response to the stimulation have been believed to have very promising potential for mapping renal nerves in order to selectively denervate sympathetic nerves and avoid futile ablations.

Using BP Response Patterns to Identify Hot Spot, Cold Spot and Neutral Spot

Based on the heterogeneous physiology of sympathetic and parasympathetic fibers, variant proportions of sympathetic and parasympathetic fibers produce different phenotypes of BP responses when stimulated. As we have discussed previously, [20] the same bundle may contain different types of nerves such as sympathetic and parasympathetic (or sympathetic inhibitory) fibers. The changes of BP in response to electronic stimulation are an integrated physiological event, depending upon which nerve fibers are dominant at this particular site. If a parasympathetic 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. Clearly, identifying BP patterns when stimulated could be a key for renal mapping and selective RDN.

Animal Data:

In animal studies, we [19] observed at least five patterns of BP responses which might potentially help us to distinguish sympathetic or parasympathetic-dominant sites (Figure 4).

Pattern 1: BP immediately increased to its plateau in responses to renal nerve stimulation, maintained at a steady and elevated status during the stimulation, indicating that the renal sympathetic nerve is dominant in this site. We presumed that electrical stimulation signals were transmitted to the central nerve system (CNS) via afferent fibers and increased central sympathetic activity, leading to an increasing central sympathetic output to the entire body. It caused a series of physiological effects, including peripheral vasoconstriction, increases in myocardial contractility and cardiac output, resulting in BP elevation. Efferent nerve fibers in the same bundle were also captured by electronic simulation; the efferent sympathetic signals to kidneys participated the elevation of BP by renal artery contraction, release of renin from juxtaglomerular cells, and by increasing tubular sodium and water reabsorption. Overall, this pattern of BP response represents a hot spot and an ablation is needed.

According to the character of increased BP response and its quick response to stimulation, we named this pattern as Sympathetic Dominant/Rapid Response. A typical original tracing of BP in this pattern is shown in Pattern 1, Figure 4.

Pattern 2: BP was transiently declined below baseline and then increased to achieve a steady and elevated status above baseline in responses to renal stimulation. We believed that this pattern represents simultaneous activations of sympathetic and vagal nerves. Because the transmitted

speed of vagal fibers to the CNS is faster than that of afferent nerves, the BP firstly decreases and then gradually increases. The net effect results in elevated BP, indicating that the impacts of sympathetic nerves on BP are more dominant than those of vagal nerves. This site is a hot spot and should be ablated.

Because of the increased but delayed elevation of BP, this pattern is named as Sympathetic Dominant/Slow Response, showing in Pattern 2, Figure 4.

Pattern 3: BP immediately decreased below baseline in responses to renal stimulation and maintained at the low level in a steady status during the stimulation. This pattern represents a site with dominant parasympathetic nerves, which belongs to a cold spot and should not be ablated. Ablation of such sites may lead to inhibition of parasympathetic nerve activity and promotion of sympathetic nerve activity, resulting in BP elevation.

We named this pattern as Parasympathetic Dominant/Rapid Response and an example of such a pattern is shown in Pattern 3, Figure 4.

Pattern 4: BP was transiently declined below baseline in response to renal stimulation and then went up but stayed a level below baseline during the stimulation. This pattern of BP also represents simultaneous activation of sympathetic and parasympathetic nerves; however, the integrated effects of these two nerve types maintain BP at a low level, indicating the dominant function of parasympathetic nerves. This is a cold spot and should not be ablated.

Since BP achieves a low level at a steady state in a slow manner, the pattern is named as Parasympathetic Dominant/Slow Response, an example is shown in Pattern 4, Figure 4.

Pattern 5: BP was fluctuated around baseline level in response to renal stimulation but the fluctuation was within 5 mmHg beyond or below baseline during the stimulation. This pattern represents a site in which there is no renal nerve or a well balanced and integrated function

between sympathetic and parasympathetic nerves. Since BP was not changed, this site plays a minor role in BP regulation and, therefore, presents a neutral spot and should not be ablated.

This pattern of BP is named as Neutral Response. An example of this pattern is shown in Pattern 5, Figure 4.

Preliminary Human Data:

BP response patterns due to renal stimulation are more complicated in a clinical setting. We have observed at least six different patterns in responses to renal stimulation representing hot, cold and neutral spots, respectively. To best illustrating these patterns, graphs are shown in Figure 5. Here, the elevation or reduction in BP was defined as the change of systolic BP (SBP) once it was ≥5mmHg from baseline.

Pattern 1: SBP is directly increased from baseline and maintained at an elevated level. This pattern is easily assessed as a hot spot and needs to be ablated.

Pattern 2: SBP fluctuated in the manner of repeatedly increasing and then decreasing, or vice versa; however, the overall increases in SBP were above baseline more than 5mmHg. We believe that baroreflex plays a big role in the fluctuations of BP. This is a hot spot and needs an ablation.

Pattern 3: SBP transiently decreased below baseline and then increased beyond baseline, and was maintained at an elevated steady level. This is a hot spot and needs to be ablated.

Pattern 4: SBP is persistently decreased below baseline during renal stimulation. This is a cold spot and should avoid ablation.

Pattern 5: SBP transiently increased beyond baseline then decreased persistently below baseline when renal stimulation was performed. This is a cold spot and should avoid for ablation.

Pattern 6: SBP did not change much in response to renal stimulation and fluctuated around baseline. This is a neutral spot and should not ablate.

Apparently, the response patterns of BP to renal stimulation in human are more complicated than in animals. Although the underlying mechanisms responsible for these patterns are not fully understood and need to be further revealed; analyzing and distinguishing these BP response patterns to renal stimulation will help operators to identify nerve types and determine sites to ablate or not ablate.

Renal Mapping and Ablation System

The combined renal mapping and ablation system developed by SyMap Medical (Suzhou), Ltd (Suzhou, China) is consisted of a dedicated electromapping/ablation SyMapCath I™ catheter and a SYMPIONEER S1™ Stimulator/Generator [27]. The stimulation/ablation catheter has a steer tip and is within a sheath that can be manipulated to go forward/back and turn 90 degrees in the sheath via a catheter handle. The sheath can be used for contrast injection (Panel A, Figure 6) as this design provides conveniences for operators without using additional accessories. The stimulator/generator can perform both electronic stimulation and RF ablation with the catheter (Panel B, Figure 6). This system could facilitate appropriate patient selection through screening for candidates whose BP is driven by renal sympathetic nerve activity. This would allow the operators to target only optimal ablation sites (hot spots/sympatho-stimulatory) while minimizing damage to cold spots/sympatho-inhibitory sites, with documentation of technical success through the loss of systemic BP changes when stimulated again after RDN.

SMART Study and Preliminary Results

The ongoing Sympathetic Mapping/Ablation of Renal Nerves Trial (SMART Study, ClinicalTrials.gov ID: NCT02761811) aims to evaluate the safety and efficacy of targeted renal sympathetic denervation using the system in patients with pharmacotherapy and uncontrolled hypertension for at least 6 months, and then after standardized antihypertensive drug therapy (at

least two classes of drugs) for at least 28 days while office systolic BP is still ≥ 150mmHg and ≤180mmHg.

Two major questions need to be answered after RDN procedure: How much blood pressure will be decreased and how many antihypertensive drugs will be taken less? The current designs of clinical trials are focused on the former and data have emerged for this question; the latter, however, has not been answered or even paid enough attention. We believed that changes of antihypertensive drugs should be a major clinical endpoint for RDN trials. The views of Weber et at. supported our ideas and they pointed out that an important endpoint for RDN trials is to test whether patients receiving the procedure have a reduced need for additional antihypertensive drugs in order to achieve optimal treatment targets [28]. In a clinical setting, the design using reduction in BP as a major clinical endpoint has a challenge to be taken: convincing patients to follow drug compliance even as their BP is still ≧150mmHg after RDN, and this is particularly difficult to maintain drug compliance for patients in sham group during a six-month follow-up period. If patients in sham group take any antihypertensive drugs to manage their high BP, the difference of office systolic BP between RDN and sham group could be compromised since the efficacy of global RDN is around 10 mmHg [6,9,10].

Thus, we designed dual primary endpoints at 6 months after RDN for SMART study:

1. The control rates of office systolic blood pressure (SBP<140mmHg)
2. The composite index of antihypertensive drugs

The Composite Index is derived from the numbers of antihypertensive drugs and doses of the medications as below:

Drug Composite Index = Weights × (sum of doses)

Weights is the number of classes of antihypertensive drugs.

One standard dose is defined as 1, a half dose is defined as 0.5, and double dose is defined as 2.

For instance, if a patient takes one dose of an angiotensin II receptor blocker and one dose of a calcium blocker, this patient's Drug Composite Index is: 2×(1+1)=4.

Via this trial, we will be able to tell patients and physicians how many antihypertensive drugs are taken less after RDN.

During the RDN procedure, renal mapping and selective denervation are performed. Renal nerve stimulation is delivered for 60 seconds at 15mA, 20 Hz and pulse duration of 5ms, and hot spots are ablated for two minutes at 8-10 watts and 50℃. If an unsatisfied RDN is found，which can be confirmed by a post procedure stimulation and BP response remains, a repeat RDN is needed on the same site.

This is a prospective, multicenter, single blind, randomized and controlled trial, and patients will be informed, given consent and entered into a screening process. During the screening period, patients will receive a standardized antihypertensive drug treatment for at least 28 days and office BP is still ≥ 150mmHg, and ≤180mmHg, and meet the inclusion and exclusion criteria. These patients will conduct renal artery angiography and are allocated to either renal sympathetic nerve denervation group or renal artery angiography group by a randomizing system in a 1:1 ratio (220 patients, 110 pairs). Patients with office BP that haven't achieved an ideal level (<140 mmHg) three months after RDN will titrate doses and/or classes of antihypertensive drugs according to a predefined standardized medication regimen until their office BP <140 mmHg. All medications are provided by the study sponsor (SyMap Medical (Suzhou), Ltd.) and titrated antihypertensive drugs must be only chosen from the standardized drug regimen (Table 3). The class/dose and order to titrate antihypertensive drugs are rigorously defined. Physicians who perform post-procedure patient management and physicians who perform RDN procedures are

blind to each other. Patients will be followed for 7 days after the procedure or at discharge from hospital, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 9 months and 12 months. Urine samples will be collected at the end of each screening, 3 months, 6 months and 12 months to monitor and maintain the antihypertensive drug compliance of these patients.

Preliminary data from SMART Study were presented at CRT 2017 (Washington DC) [29] and TCT 2019 (San Francisco, USA) [30], and confirmed some of the theoretical groundwork and preliminary data laid out as above. In ten patients with uncontrolled hypertension, only 54% of sites were responsive to renal stimulation with BP elevation (hot spots) (Table 1). Maybe most importantly, stimulation resulted in a BP drop in 16% of sites (systolic BP − 16 mmHg, diastolic BP −4 mmHg, and mean BP− 7 mmHg in average) (Table 2) and no BP response to stimulation in 29% of sites. Ablation of the hot spots prevented BP elevation with repeat stimulation intra-procedurally, which confirmed an effective RDN. Otherwise, a second ablation would be needed on the same site. Long-term outcomes in the full study cohort are still pending. Similar attempts to develop a mapping system were also made by Rainbow/Pythagoras (Israel). Preliminary results were recently presented by Mahfoud, Tsioufis, and Damen at EuroPCR 2017 and confirmed a heterogeneous response to a renal nerve stimulation based on locations of stimulations, with a tendency towards higher BP elevation and higher levels of energy in more proximal renal artery locations [23, 31]. The continued development of appropriate tools to test the renal nerve contribution to elevated BP confirms the technical success of RDN, and in the end allows targeted RDN, which appears to be in close reach.

The promise of a targeted, selective sympathetic RDN opens up a number of possibilities which could address the limitations previously experienced with the conventional approach of unselective or global RDN. Dedicated clinical studies will need to prove the safety and efficacy of the selective RDN approach on long term BP reduction.

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Figure Legends

Figure 1. Panel A shows the renal sympathetic renal plexus of a human right kidney. (A) Anterior view and (B) posterior view. 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).

Panel B shows stained slides of the same artery and segment for immuno-histological markers. The upper left corner is the lumen of the artery. (a) TH, marker for sympathetic, (b) NOS, marker for parasympathetic, (c) CGRP, marker for afferent, (d) PGP, marker for general marker. TH (tyrosine hydroxylase), NOS (nitric oxide synthase), CGRP (calcitonin gene related peptide), PGP (Protein Gene Product 9.5).

Adapted with permission from van Amsterdam et al. (16) and Mompeo et al. (17).

Figure 2. Theoretical framework for selective vs global renal denervation: red lines/dots represent "hot spots" - pressor spots. These are nerves that raise the blood pressure when stimulated. These spots are the ideal targets of renal denervation. Green line/spots represent "cold spots" - inhibitory spots, which lower the blood pressure when stimulated. The nerve fibers in yellow are neutral in their contribution for blood pressure regulation and do not show hemodynamic effects when stimulated.

Adapted with permission from Fudim et al. (18)

Figure 3. Difference in nerve distribution between strong-response site (SRS) which increased blood pressure significantly when stimulated, and weak-response site (WRS) which increased blood pressure much less when stimulated. A and B, Representative Masson staining image for SRS and WRS. The red arrows indicated renal nerve bundle, and the black arrows indicated ablation

area. The total area (C) /number (D) of renal nerves in SRS were greater than that in WRS. There was no difference in distance (E) from lumen to nerve between SRS and WRS.

Adapted with permission from Liu et al. (20).

Figure 4. The different types of blood pressure patterns in responses to renal stimulation in dogs. Adapted from Tan et al (19)

Figure 5. The different types of BP patterns in responses to renal stimulation in human.

Figure 6. Renal Mapping and Ablation System developed by SyMap Medical Ltd., consisted of SyMapCath I™ catheter (A) and SYMPIONEER S1™ Stimulator/Generator (B).