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Catheter Based Renal Nerve Ablation as a Novel Hypertension Therapy: Lost, and Then Found, in Translation

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Keywords

Hypertension; renal nerves; renal denervation

Introduction

The hypothesis that renal nerves mediate, at least in part, the pathogenesis and maintenance of hypertension is based on decades of preclinical studies and, to a certain extent, recent clinical trials of catheter-based renal nerve ablation (CBRNA) in humans. The first two clinical trials for CBRNA, Symplicity HTN-1 and Symplicity HTN-2, reported sustained reductions in arterial pressure in patients with drug-resistant hypertension and set the stage for the first blinded U.S trial, Symplicity HTN-3. However, Symplicity HTN-3 failed to reach its 6-month efficacy endpoint thus jeopardizing the clinical application of CBRNA in the United States.

The goal of this article is to reexamine the feasibility of CBRNA to treat hypertension. Preclinical studies on the role of renal nerves in hypertension have been extensively reviewed[1, 2], as have the Symplicity HTN-1, 2, and 3 trials [3–567]. Therefore, we will review these topics only briefly to provide context for the primary purpose of this article which is to answer the following question; is the outcome of Symplicity HTN-3 due to the failure to translate preclinical knowledge to the clinic, or, is our basic understanding of the mechanisms by which renal nerves contribute to hypertension flawed?

Rationale for Renal Nerve Ablation to Treat Hypertension

The kidney is innervated by sympathetic *efferent* fibers that modulate three pharmacological targets for the treatment of hypertension: renin release, tubular sodium reabsorption, and renal vascular resistance[1, 2]. Although conventional pharmacological treatments of these targets lower arterial pressure, patients often present with negative side effects which may lead to drug incompliance. One rationale for CBRNA is that this treatment would suppress

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DISCLOSURES

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renin release, tubular sodium reabsorption, and renal vasoconstriction, while avoiding the side effects associated with more globally acting pharmacotherapies.

The kidney is also innervated by renal *afferent* fibers that provide the central nervous system sensory information related to the *internal milieu* of the kidney [1, 8, 9], and their activity may contribute to hypertension by modulation of renal and global sympathetic outlfow[1, 8, 10]. Afferent and efferent nerves are intermixed such that CBRNA destroys both, so it is impossible to know which contribute to the antihypertensive response to this treatment.

Emergence of CBRNA: The Symplicity HTN Trials

Since the lumen of the renal artery is readily accessible by an intravascular catheter, and renal nerves travel along the walls of the renal artery, they are readily accessible for ablation using catheter-based technology. The first proof-of-principle for CBRNA was the Symplicity HTN-1 trial conducted in 45 patients with drug resistant hypertension[3, 4]. CBRNA was performed using the Symplicity Flex percutaneous radiofrequency ablation catheter. Mean office blood pressure before denervation was 177/101 mmHg, and was decreased at 1 month (-21/-10 mmHg) and up to 36 months (-32/14 mmHg) after a single procedure. Symplicity HTN-2 was a larger randomized control trial in 106 patients with drug resistant hypertension conducted in 24 centers in Europe, Australia and New Zealand[5]. Patients were randomized 1:1 for treatment or control, but control subjects did not receive a sham procedure. The results of this trial were similar to Symplicity HTN-1, where a sustained decreased in office blood pressure was observed in patients treated with CBRNA compared to controls.

The outcome of a larger U.S. randomized, blinded, sham-controlled trial, Symplicity HTN-3, was highly anticipated. Symplicity HTN-3 was conducted in 535 patients randomly assigned in a 2:1 ratio to undergo CBRNA (N=364) or a sham procedure (N=171). CBRNA decreased office systolic blood pressure (SBP) by an average of 14mmHg six months post-CBRNA. However, the primary efficacy endpoint was not met as the decrease in office SBP was not different between the CBRNA and the sham group (−11mmHg)[6], suggesting either a placebo or Hawthorne effect.

An extensive post-hoc analysis of Symplicity HTN-3 suggests failure to properly perform the procedure may have been major factor in the failure of the trial[11]. In addition, 39% of patients changed medication during the trial, which may have influenced responses[11]. Moreover, African-Americans in the sham control group receiving a vasodilator had a marked decrease in systolic pressure (−21.9 mmHg) that was not observed in the other subgroups, perhaps reflecting a change in pharmacological adherence[11]. The issue of drug resistance and adherence to medication was recently addressed in the superbly well-designed DENERHTN trial[12]. This open-label randomized controlled trial with blinded endpoint evaluation was conducted in 15 French centers in patients with resistant hypertension. In order to verify that patients were drug resistant, a combination of 1.5 mg indapamide, 10 mg ramipril (or 300 mg of irbesartan) and 10 mg of amlodipine was administered for 4 weeks during which time *ambulatory* blood pressure was measured. Patients were then randomized 1:1 and assigned to receive either standardized stepped-care antihypertensive treatment (SSAHT) alone or SSAHT and renal denervation. SSAHT involved the addition of 25 mg

spironolactone, 10 mg bisoprolol, 5 mg prazosin and 1 mg rilmenidine for 3 months if home and ambulatory blood pressure were greater than 135/85 mm Hg. Ambulatory systolic pressure decreased 9.9 mm Hg in the control (SSHAT) group and 15.8 mm Hg in the renal denervation + SSHAT group. More importantly, it was reported that the number of anti-hypertensive drugs and *drug adherence* at 6 months was similar in both groups. These investigators concluded that, in patients with *well-defined* resistant hypertension, renal denervation decreases blood pressure more than optimization of drug therapy alone and that "this additional blood pressure lowering effect may contribute to a reduction in cardiovascular morbidity if maintained in long term after renal denervation"[12]. These findings, as well as the issues raised in the Symplicity HTN trials raised several questions regarding CBRNA as a therapy for hypertension. We attempt to address some of these questions in the following sections.

Questions Raised by the Symplicity HTN Trials

Is the arterial pressure response to RDN due to ablation of efferent or afferent renal nerves?

It has been reported that CBRNA had no effect of plasma renin and aldosterone[13]. However, the expected decrease in renin release caused by CBRNA may be offset by the direct effect of reduced renal perfusion pressure to stimulate renin release[1]. These investigators also reported that CBRNA decreased total peripheral resistance whereas cardiac output did not change[13]. It is not known whether the decrease in peripheral resistance was due to reduced renal vascular resistance specifically, or whether vasodilation occurred in other vascular beds. CBRNA reportedly reduces renal resistive index with no change in glomerular filtration rate[14].

The hypothesis that *afferent* renal nerves contribute to the effects of CBRNA was sparked by clinical studies showing that CBRNA had off-target effects, including reduced fasting plasma glucose, decreased muscle SNA, lower sleep apneic frequency, and less cardiac arrhythmias[15–17]. These findings are consistent with preclinical studies demonstrating that sensory neural signals from kidneys modulate sympathetic activity not only to the kidney and other organs[1].

Techniques to ablate afferent renal nerves, independent of efferent nerves, have been used to study experimental hypertension. The first method was bilateral sectioning of the spinal dorsal roots from T9-L1, or dorsal rhizotomy (DRZ). This method interrupts renal sensory input to the spinal cord, has been reported to attenuate several models of experimental hypertension[1]. However, DRZ is not specific for *renal* afferent nerves since cutaneous, somatic, and all other visceral afferent inputs between T9 and L1 are also sectioned by this method. This is a confounding factor, particularly in salt-sensitive models of hypertension, since animal and human studies have shown the skin and skeletal muscle store sodium and may be important in sodium homeostasis[18].

We recently developed a chemical ablation method that targets renal afferent nerves while leaving renal efferent nerves and other sensory afferent nerves intact[19]. This method attenuates the development of deoxycorticosterone acetate – salt (DOCA-salt) hypertension

in the rat just as effectively as total (efferent+afferent) surgical RDN[19, 20]. This finding combined with the observation that basal afferent renal nerve activity was 2.5-fold higher in DOCA-salt compared to normotensive control rats[20] suggests this model is driven by afferent, not efferent, renal nerves. However, it is important to note that this method of targeted afferent renal nerve ablation has no effect on another model of hypertension, the Dahl-salt sensitive rat, despite the fact that complete RDN lowered arterial pressure[21]. These data suggest the response to RDN in this model is mediated by ablation of efferent, not afferent, renal nerves. The same is true for the AngII-induced mouse model in that RDN attenuates hypertension, but afferent renal nerve ablation does not [22]. When combined, these studies indicate the role of efferent and afferent nerves to the pathogenesis of hypertension are model-dependent.

Does RDN decrease sympathetic nerve activity to other organs?

Some hypertensive patients have increased muscle SNA (MSNA)[23–26]. In one case report, multi-unit MSNA decreased from 56 bursts/min to 41 bursts/min one month after CBRNA, and 19 bursts/min 12 months thereafter[27]. Another study did not find a reduction in MSNA following CBRNA, but they also did not observe a decrease in arterial pressure[28]. A subsequent study by another group measured both multi-unit and *single-unit* MSNA, before and three months after CBRNA. There was a modest, yet statistically significant, reduction in multi-unit MSNA from 79 to 73 bursts/100 heart beats three months after CBRNA. It was notable that *all properties* of single unit activity (spikes/100 heart beats, firing probability, and multiple firing incidence) were also markedly reduced[17], and these responses were sustained one year after RDN[29].

Grassi and colleagues measured cardiovascular and MSNA responses before and after CBRNA[30]. Although arterial pressure showed a significant decrease at 1-month post CBRNA, multi-unit MSNA did not decrease until 3 months post-ablation. Importantly, they found that the arterial pressure response *preceded* changes in baroreflex function as well. Based on this temporal response they concluded the arterial pressure response to CBRNA was not due to alterations in central sympathetic drive[30]. However, single-unit MSNA was not analyzed in this study. Since measurement of SNA in humans is currently possible only in skeletal muscle and skin[31], the effect of CBRNA on other SNA to other vascular beds is unknown.

The extent to which RDN affects SNA in unanesthetized animals has not been investigated extensively. Rossi and colleagues measured the response of renal SNA in the 2K1C rat Goldblatt model before and after RDN[32]. Six weeks following induction of renal artery stenosis in the right kidney, SNA to the left kidney was three-fold higher in 2K1C rats compared to controls. RDN of the clipped kidney decreased arterial pressure, renal SNA, and renal AngII in the contralateral kidney as well as plasma AngII[32]. These findings support the hypothesis that renovascular hypertension is due to activation of renal afferent nerves from the ischemic kidney, which drives efferent renal SNA to the contralateral kidney. Whether the increased SNA is renal-specific, or reflects an increase in SNA to other organs, remains to be investigated.

How effectively does CBRNA denervate the human kidney? Is there relationship between the efficacy of denervation and the arterial pressure response?

Data from the Symplicity HTN trials suggest a direct relationship between the number of ablations/renal artery (typically 4–6) and the decrease in arterial pressure, thus implying the more extensive the denervation the larger the fall in arterial pressure[11]. This is supported by animal studies showing the extent of RDN and the fall in arterial pressure are linearly correlated[1, 33]. A major limitation of CBRNA is the lack of a method to confirm completeness of denervation. It has been shown in a research setting, using renal norepinephrine spillover as a measure of renal SNA in humans, that even in the hands of expert interventionists, there is variability in the completeness of denervation using the single electrode Symplicity catheter[7]. On average the denervation was 45% effective with a range of 0–80%[7].

With that in mind, it is important to note that all interventionists for Symplicity Flex HTN-1,2 trials were properly trained by medical staff *before* the trials began. In contrast, none of the 111 interventionists at the 88 U.S. centers received hands-on training by medical staff prior to Symplicity HTN-3[7]. Instead, training was provided by company staff rather than experienced interventionists in previous trials[7]. More than 50% of the operators in Simplicity HTN-3 performed at most two procedures and 31% performed just one[7].

Finally, another obstacle to achieving complete denervation is that the secondary branches of the renal artery, as well as accessory renal arteries, are also innervated which can elicit a substantial pressor response when activated in humans[34]. Targeting these vessels, in addition to the main arteries, could lead to an improved denervation efficacy as further discussed below.

Taken together, these clinical and preclinical studies suggest: 1) the more extensive the denervation the greater the fall of arterial pressure, and 2) previous catheter-based technology did not consistently achieve complete denervation of the human kidney.

Do the kidneys reinnervate after renal nerve ablation?

If the arterial pressure decrease following RDN is directly related to the extent of denervation, then will reinnervation result in arterial pressure returning toward control over time? This does not seem to be the case in that patients from the Symplicity HTN-1 trial have demonstrated a gradual further decrease in arterial pressure over the course of a year, which has been stable for three years post-CBRNA.

Booth and coworkers assessed anatomical and functional reinnervation of normotensive sheep kidneys 5.5 and 11 months following CBRNA using the Symplicity Flex catheter [35]. By 11 months following CBRNA, the anatomical distribution and functional responses of efferent and afferent renal nerves were completely restored[35]. The authors suggest that their findings challenge the concept that the prolonged response to CBRNA in humans is due to sustained RDN. Based on these findings, Phillips speculated the sustained arterial pressure response to CBRNA could be the result of temporary loss of afferent renal nerve activity resulting in long-term changes in set points of sympathetic reflex pathways[36].

Do biomarkers exist to identify candidates that will respond to CBRNA?

Many of the unresolved issues surrounding CBRNA could be solved if there was a reliable test or biomarker to indicate the contribution of renal nerves to hypertension. With this goal in mind, Dorr and colleagues measured plasma levels of three indicators of vascular damage, soluble fms-like tyrosine kinase (sFLT-1), intracellular cell adhesion molecule (ICAM-1), and vascular cell adhesion molecule (VCAM-1) in 55 patients before and 6 months after CBRNA[37]. A significant mean office systolic pressure reduction of 31.2 mmHg was observed in 46 patients (84%) who were classified as “responders”. On the other hand, 9 patients (16%) were classified as “non-responders” with a mean office systolic pressure reduction of 4.6 mmHg. Responders had significantly higher serum levels of sFLT-1, ICAM-1 and VCAM-1 at baseline compared to non-responders, suggesting these serve as biomarkers to predict responsiveness to CBRNA[37]. However, it has been suggested that this is a small sample from a single center, and, importantly, these biomarkers did not respond to CBRNA[38] so further investigation is required.

Another methodology was described by de Jong and colleagues[39]. In this study, 14 patients with drug-resistant hypertension underwent electrical renal nerve stimulation (RNS) to measure the acute pressor responses before and immediately after CBRNA under general anesthesia[39]. Prior to CBRNA, systolic pressure increased 50mmHg with RNS and this was decreased to 13mmHg immediately after. More importantly, there was a strong and significant positive correlation between the systolic pressure response to RNS and response of ambulatory blood pressure at three and six months post-CBRNA[39].

To the best of our knowledge, there are no preclinical studies to date that have identified a reliable biomarker or test to predict the responsiveness to RDN in preclinical models of hypertension.

The SPYRAL HTN Global Clinical Trial Program

Despite the strong preclinical foundation supporting the concept of RDN to treat hypertension, and the positive results of the Symplicity HTN-1,2 trials, the failure of Symplicity HTN-3 initially led some to doubt CBRNA as an effective treatment for hypertension. However, based on the discussion above we strongly feel that the failure of Symplicity HTN-3 was almost entirely the result of technical and procedural pitfalls. Indeed, findings from other clinical trials using improved catheter designs[40–45] as well as other technologies for ablation such as high-intensity focused ultrasound[46], provide further support that RDN has great promise as a novel therapeutic approach to treat hypertension.

Early results from the SPYRAL HTN Global Clinical Trial Program support our conclusion. This trial was specifically designed to avoid the pitfalls of Symplicity HTN-3[47] from both clinical trial design as well as the catheter technology. The trial consists of two simultaneous, randomized, sham-controlled trials conducted by skilled interventionists at 25 centers in the United States, Japan, Europe and Asia. One arm of the trial will be conducted in patients on three medications; a thiazide diuretic, an ACEI antagonist, and a calcium channel blocker, whereas the other, SPYRAL HTN-OFF MED, will be conducted in patients either not on medication or following a 3-month washout period.

A key feature of the 4-electrode Symplicity Spyral catheter design, compared to the single electrode Symplicity Flex catheter, is the capability of performing ablations in branches as small as 3mm in addition to the main renal artery. As a result, whereas the Symplicity Flex catheter treats only the main renal artery, achieving 4–6 ablations/renal artery (or 8–16 ablations/patient) the Symplicity Spyral catheter can achieve approximately 4 times that number of ablations including branch arteries. This should result in a more effective and consistent denervation and, based on preclinical studies showing a direct correlation between the extent of denervation and the fall in blood pressure[33], a greater antihypertensive response.

The 3-months results from the SPYRAL HTN-OFF MED trial are promising in that CBRNA statistically decreased office systolic (−10 mmHg) and diastolic (−5.3 mmHg) pressure in contrast to Sham controls in which there was no significantly change[48]. Moreover, the average number of ablations/patient was 43.8 ± 13.1 with 17.9 ± 10.5 in the main renal arteries and 25.9 ± 12.8 in branches[48]. It important to note that the combination of main renal artery and branch ablations resulted in larger decreases in arterial pressure than main artery ablations alone[49]. These new findings are very encouraging and provide strong support for the concept that, if done properly, CBRNA does decrease arterial pressure in humans.

Device-Based Renal Denervation as a Novel Hypertension Therapy: Lost, and Then Found, in Translation?

We conclude by answering the question we posed at the beginning of this article: Is the outcome of Symplicity HTN-3 due to the failure to translate preclinical knowledge to the clinic, or, is our basic understanding of the mechanisms by which renal nerves contribute to hypertension flawed? We firmly believe that the failure of Symplicity HTN-3 was simply a case of “lost in translation”. It is now clear that weaknesses in the trial design such as unregulated medication adjustments, improper training of interventionalists, catheter design, and the lack of a method to confirm denervation resulted in the failure of Symplicity HTN-3[7]. With the emergence of improved catheter designs to minimize “operator error”, proper training of interventionists, and rigorous trial design such as the SPYRAL HTN Global Clinical Trial Program, we predict that CBRNA will be “found in translation” and emerge as an effective therapy for the treatment of hypertension and other clinical conditions associated with chronically elevated sympathetic activity. In fact, a recent clinical study demonstrated that, in addition to decreasing MSNA, CBRNA reduced monocyte activation, monocyte platelet aggregation, and circulating levels of several inflammatory cytokines and chemokines in hypertensive patients suggesting a direct connection between sympathetic activity and low-grade inflammation[50]. This represents yet another important area of investigation regarding the clinical benefits of CBRNA.

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