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Targeting the Sympathetic Nervous System Critical Issues in Patient Selection, Efficacy, and Safety of Renal Denervation

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● Online Data Supplement

Evidence has accumulated during the past several decades, strongly suggesting that abnormalities of the sympathetic nervous system contribute to the development and maintenance of multiple disease states, including hypertension, heart failure, diabetes mellitus, sleep apnea, kidney disease, and atrial fibrillation.¹ The renal nerves have been identified as important contributors to the development of hypertension in both experimental animals and humans.² Patients with essential hypertension and other disease states often have increased efferent sympathetic drive to the kidneys as demonstrated by elevated rates of renal norepinephrine spillover.^{1,2} In addition to increased renal efferent nerve activity, there is indirect evidence for increased renal afferent activity in patients with essential hypertension.³ Nonspecific surgical sympathectomy has been effectively used as a treatment for severe hypertension,⁴ with a remarkable difference in outcomes at 5 years of follow-up. Recently developed endovascular catheter technology has allowed selective denervation of the human kidney using radiofrequency (RF) energy delivered via the renal artery lumen.⁵ Although the initial clinical trials with this minimally invasive technique have documented the safety and efficacy of such an approach, critical questions have been raised pertaining to long-term safety, mechanisms of action, appropriate patient selection, reductions in ambulatory blood pressure (BP), definition and level of responder rates, need for identification of characteristics that predict nonresponse, phenomenon of a delayed response, and several others.⁶ Here, we address several of these key questions.

What Are the Mechanisms Responsible for a Decrease in BP After RDN?

Catheter-based renal nerve ablation interrupts both efferent and afferent nerves (Figure 1). It is well established that activation of renal sympathetic efferents can decrease renal blood flow, increase tubular sodium and water reabsorption, and increase renin release.² However, there is emerging evidence that renal afferent signaling may be as important as renal efferent activity in elevating BP. Activation of renal afferents can cause a

reflex increase in sympathetic tone to the kidneys and other organs.⁷ Intrarenal infusion of bradykinin in conscious rats⁸ or intrarenal infusion of adenosine in conscious dogs with unilateral nephrectomy⁹ causes an immediate increase in BP that was abolished by surgical renal denervation (RDN). A role for renal afferents in rats with renovascular hypertension was indicated by a significant drop in BP after dorsal rhizotomy (T8 or T10 to L2) to exclusively interrupt afferent fibers.¹⁰

There is also evidence that renal afferents play a role in mediating an increase in sympathetic tone in humans. In 25 patients with treatment-resistant hypertension, RDN significantly decreased multi- and single-unit muscle sympathetic nerve activity at 3-month follow-up, which was accompanied by a significant reduction in BP.¹¹ More recently, it was shown that the reduction in muscle sympathetic nerve activity was sustained for ≥ 1 year after the procedure.¹² These results provide strong evidence that the interruption of renal afferents results in a global decrease in sympathetic tone that reduces BP in patients with resistant hypertension.

In contrast, a study of 12 patients with milder resistant hypertension and less pronounced sympathetic activation showed no significant change in BP, mean muscle sympathetic nerve activity, or heart rate variability at 3 or 6 months after RDN, although individual responses were variable.¹³ Although an association between a reduction in BP after RDN and a decrease in global sympathetic tone is apparent, more studies are needed to determine the relative importance of afferent and efferent nerves in mediating the changes in BP with RDN.

What Is the Efficacy of RDN in Treating Resistant Hypertension?

In 2009, the results of the first proof-of-principle multicenter study from 45 patients with treatment-resistant hypertension who underwent catheter-based RDN were reported.⁵ The initial cohort was subsequently expanded from 45 to 153 patients, and the follow-up duration was increased to a minimum of 2 years (Symplicity HTN-1).¹⁴ The mean baseline office BP in the expanded cohort was 176/98 mmHg while patients were

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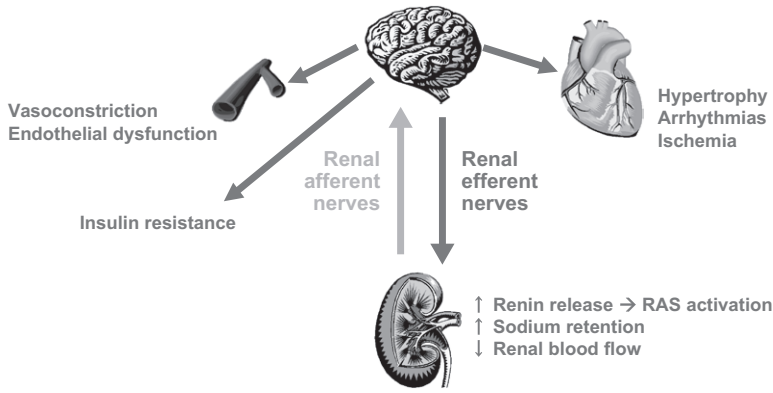


Figure 1. The kidney can be both the recipient and the origin of increased sympathetic tone. Renal sympathetic efferent activation affects the ability of the kidneys to regulate blood pressure, whereas activation of some types of renal afferents can cause a global increase in sympathetic tone. RAAS indicates renin-angiotensin-aldosterone system.

on an average of 5.1 ± 1.4 antihypertensive drugs. The average reductions in office BP were 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months after RDN, respectively.

Because there was no control group in Symplicity HTN-1, a subsequent trial (Symplicity HTN-2) was initiated as a multicenter, randomized, controlled trial.¹⁵ The inclusion criteria were age 18 to 85 years with an office systolic BP ≥ 160 mm Hg (≥ 150 mm Hg in patients with diabetes mellitus), despite treatment with ≥ 3 antihypertensive drugs including a diuretic. There were 106 patients randomly assigned to undergo RDN combined with prior treatment (RDN group, $n=52$) or to maintain prior treatment alone (control group, $n=54$). Office BP fell by an average of 32/12 mm Hg in the RDN group at 6 months, whereas no change occurred in the control group (1/0 mm Hg). At 6 months, 41 (84%) of 49 patients who underwent RDN had a reduction in systolic BP of ≥ 10 mm Hg compared with 18 (35%) of 51 controls. The systolic BP fell to <140 mm Hg in 19 patients in the RDN group. After 6 months, 35 patients in the control group crossed over to receive RDN, and these patients experienced a significant drop in BP similar to that observed in the initial RDN group. Analysis of the data from all the patients who underwent RDN showed that there was a sustained reduction of BP out to 1 year.¹⁶ Most recently, further follow-up of the entire Symplicity HTN-2 population showed that the reduction in office BP was sustained during 2 years (Figure 2).

Of note, ambulatory BP monitoring (ABPM) was not mandatory in Symplicity HTN-1 and HTN-2, and office BP was used as an entry criterion. This design could have allowed inclusion of patients with a white-coat component contributing to their hypertension. Although the limited ABPM data

available for Symplicity HTN-2 did demonstrate a significant reduction in BP after RDN, the magnitude of the effect was less pronounced than office BP reduction. Potential reasons for this are discussed below.

A third multicenter, randomized, controlled trial (Symplicity HTN-3) with similar inclusion criteria has completed recruitment recently.¹⁷ ABPM was mandatory, and patients were excluded if their average ABPM was <135 mm Hg. All patients were blinded to randomization using sedation, sensory isolation, and lack of familiarity with the procedure. Furthermore, all patients had a renal angiography, and eligible subjects were randomly assigned at a 2:1 ratio to either the RDN or the control group. The primary outcome is the difference in the change of office-based systolic BP at 6 months, with differences in average ABPM reduction as a secondary outcome. First results are expected to be available in early 2014 and will be relevant to determine the future role of RDN for resistant hypertension in clinical practice.

What Patient Cohorts With Hypertension Are Likely to Benefit From RDN?

The long-term effects of RDN on BP have mainly been evaluated in patients with resistant hypertension. Resistant hypertension is defined as failure to achieve the target BP in patients who are adhering to full tolerated doses of ≥ 3 drugs that include a diuretic.^{18,19} However, the apparent resistance to treatment in many patients may be pseudo-resistance rather than true resistance, because patients frequently do not adhere to their drug regimen, are not taking adequate doses, or are not on optimal combination of drugs. Pseudo-resistance may also occur in patients who have white-coat hypertension. The prevalence of true resistant hypertension among all patients treated

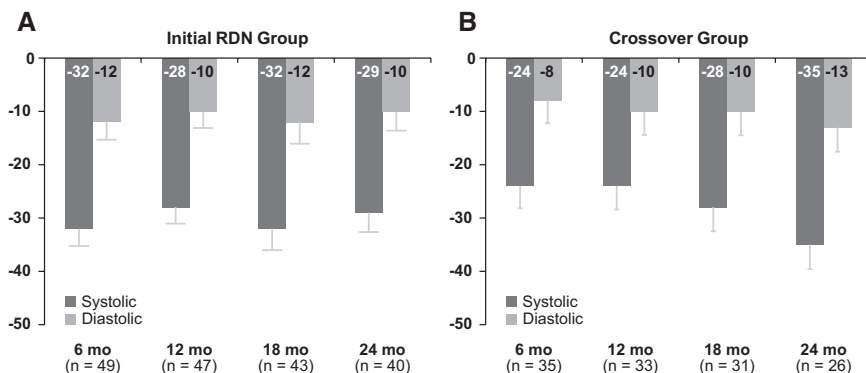


Figure 2. The changes in office blood pressure (BP) over time in Symplicity HTN-2 patients. **A**, BP changes in the initial renal denervation (RDN) group. **B**, Changes in BP in the control group that crossed over to RDN after 6 months. The data are presented as mean \pm SD.

for hypertension varies markedly among clinical trials. The National Health and Nutrition Examination Survey reported a prevalence of 12.8% in US adults treated for hypertension,²⁰ and the Spanish registry of ambulatory BP monitoring reported a similar prevalence of 14.8%.²¹ However, other large clinical trials such as ASCOT (Anglo Scandinavian Cardiac Outcomes Trial), ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), and ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) reported a prevalence ranging from 25% to 35%.²² Although the exact prevalence of true treatment resistance remains unknown, this form of hypertension most likely occurs in a substantial proportion of patients with hypertension.

Several professional medical societies have provided consensus statements with detailed criteria to define patients eligible for RDN^{23,24} (see online-only Data Supplement A). Because not all patients with resistant hypertension have a positive response to RDN (commonly defined as a ≥ 10 -mmHg decrease in office systolic BP), it would be useful if there were clinical features that could predict a positive response. In Symplicity HTN-1, multivariate analysis found that only systolic BP at baseline and the use of centrally acting sympatholytic drugs were independent predictors of a greater decrease in systolic BP.¹⁴ In a larger cohort of 346 resistant patients treated with RDN, baseline office BP was found to be the only determinant of the magnitude of the BP response.²⁵ Interestingly, a recent report indicates that impaired baroreflex sensitivity may predict the BP response to RDN, a proposition that requires confirmation in larger cohorts.²⁶

In addition to severe resistant hypertension, it is possible that RDN may be useful in patients with milder resistant hypertension. In an initial pilot study, 20 patients with an office systolic BP of 140 to 160 mmHg despite ≥ 3 antihypertensive medications were treated with catheter-based RDN.²⁷ The mean office BP at baseline was 148.4/83.0 mmHg and decreased by 5.7/0.5 and 13.1/5.0 mmHg at 3 and 6 months after RDN, respectively. Compared with baseline, the mean ambulatory BP was reduced by 11.3/4.1 mmHg at 6 months. Similarly, a recent report on a cohort of 54 patients with moderate resistant HTN (office BP $\geq 140/90$ mmHg and $< 160/100$ mmHg) on an average of 5.1 antihypertensive drugs and 24-hour ambulatory BP $\geq 130/80$ mmHg demonstrated a reduction of office BP by 13/7 mmHg 6 months after RDN.²⁸ Office BP was controlled below 140/90 mmHg in 51% of the patients, and 37% of patients reduced their antihypertensive medications. In the patients ($n=36$) who had ABPM before and 6 months after the procedure, there was a reduction in average ambulatory BP of 14/7 mmHg. Although these preliminary data are encouraging, other studies suggest that patients with milder resistant hypertension do not show a consistent drop in BP at 3 or 6 months after RDN.¹³ Randomized controlled clinical trials in these cohorts will be required to properly define the usefulness of RDN.

What Is the Safety of RDN?

Because RDN in humans involves the application of RF energy at multiple sites within each renal artery, it is important to examine the safety of this procedure. Initial work in a swine model showed that low-energy, catheter-based

denervation could ablate nerves surrounding the renal artery without causing arterial thrombosis or stenosis and with complete healing of the arterial wall lesions within 6 months.²⁹ A more recent swine study using optical coherence tomography showed acute local thrombus formation at the site of RF energy delivery that disappeared 10 days after the procedure.³⁰ The lesions also showed cell depletion and edema that also disappeared 10 days after the procedure. A recent clinical study also used optical coherence tomography to evaluate the renal arteries before and after RF ablation in 16 patients with resistant hypertension.³¹ Mild vessel spasm was observed along the entire length of the treated artery resulting in a significant reduction of the mean renal artery diameter from 4.84 to 4.37 mm. Endothelial-intimal edema was consistently observed, and local thrombus formation was evident in some of the treated renal arteries. Furthermore, 1 case of renal artery dissection was reported. These data indicate that RF-based RDN is associated with local injury and suggest that antiplatelet therapy should be used periprocedurally to minimize any potential adverse consequences.²⁴

Complications have also been monitored in the initial trials. In Symplicity HTN-1 and HTN-2, RDN was performed without major complications in 98% (201/209) of the patients enrolled.¹⁴⁻¹⁶ The following complications were reported in those 2 trials: femoral artery pseudoaneurysms ($n=3$), urinary tract infection ($n=1$), back pain ($n=1$), extended hospitalization for assessment of paraesthesia ($n=1$), hypotension that required hospitalization and medication adjustment ($n=1$), and renal artery dissection during placement of the guiding catheter ($n=1$). Bradycardia occurred in 7 (13%) patients during the procedure and were all resolved by atropine treatment. Renal vascular imaging was performed at 6 months after RDN in 130 patients, and 1 patient was identified with possible progression of an underlying atherosclerotic lesion that required no treatment. In the meantime, there have been 2 case reports of a secondary rise in BP after RDN as a result of progression of renal artery stenosis.^{32,33} However, it is not clear whether this was caused by the procedure itself or by the natural progression of renal atherosclerosis.

To exclude any potential adverse effect of RDN on renal function, estimated glomerular filtration rate (eGFR) was assessed in 64 patients who had extended follow-up in Symplicity HTN-1.¹⁴ During the first year of follow-up, there were no changes in eGFR in this cohort of patients. In 10 patients who had 2 years of follow-up, eGFR was reduced by 16 mL/min per 1.73 m², which was thought to be because of changes in diuretic therapy after the first year. Renal function was also evaluated in Symplicity HTN-2, and there were no changes in eGFR at 3 or 6 months after RDN (see Table S1 in the online-only Data Supplement).¹⁶

In another study, renal function and urinary albumin excretion were evaluated 6 months after RDN in 88 patients with resistant hypertension and compared with that of 12 patients who did undergo RDN, thereby serving as a control group.³⁴ Results from this study indicate that RDN decreased BP, renal resistive index, and the incidence of micro- and macroalbuminuria without adversely affecting eGFR or renal artery structure.

Although patients with abnormal renal function were excluded in Symplicity HTN-1 and HTN-2, there are now preliminary data to suggest that RDN is also safe and effective

in patients with hypertension with moderate-to-severe chronic kidney disease.³⁵ A study in 15 patients with stage 3 to 4 chronic kidney disease (mean eGFR, 31.2±8.9 mL/min per 1.73 m²) showed significantly improved office BP ≤1 year after RDN without worsening of renal function.

Whether RDN negatively affects the body's response to physiological stressors mediated via sympathetic nerves was addressed in a subgroup of patients from Symplicity HTN-2, who underwent cardiopulmonary exercise testing at baseline and 3 months after RDN.³⁶ There were 37 patients in the RDN group and 9 in the control group. BP during exercise was significantly lower at 3 months compared with baseline in the RDN group, but the heart rate increase at different levels of exercise was not affected. Furthermore, resting heart rate was lower, and heart rate recovery after exercise improved after the procedure. These data indicate that cardiopulmonary exercise tolerance is not negatively affected by RDN.

Another safety concern has been the occurrence of orthostatic hypotension after RDN because this was an important complication when nonselective surgical sympathectomy was used to treat severe hypertension in the past.⁴ To address this issue, tilt table testing was performed in 27 patients with resistant hypertension before and 3 months after RDN. BP and heart rate were lower during tilting after RDN, but there was no change in the incidence of presyncope or syncope.³⁷

Taken together, the available data suggest that adverse consequences of RDN affecting the body's capacity to cope with everyday physiological challenges are unlikely to occur.

Why Does RDN Affect Office BP More Than Ambulatory BP?

A subset of patients in the Symplicity HTN-2 trial (20 in the RDN group and 25 in the control group) underwent APBM at 6 months, and the mean reduction in BP was 11/7 mmHg in patients with RDN, whereas there was no significant change in controls¹⁵ Not surprisingly, the reduction in ABPM was less pronounced than the reduction in office BP. Other trials have confirmed that RDN causes greater reductions in office than ambulatory BP^{25–27,38}; however, the magnitude of the difference between office and ambulatory BP changes

seems to be somewhat more pronounced than that observed in BP-lowering trials using pharmacological approaches.³⁹

This discrepancy may be explained to some extent by the high baseline BP levels in the Symplicity trials.⁴⁰ Alternatively, RDN may have a significant effect on the white-coat component of office BP measurements. A recent analysis of 346 patients, who had both office and ABPM readings before and after RDN, demonstrated a significant reduction in 24-hour average ambulatory BP by 11.7/7.4 mmHg at 12 months after RDN in 303 patients with true resistant hypertension.²⁵ In contrast, 43 of the 346 patients had pseudoresistant hypertension as a result of a white-coat effect, and although RDN significantly decreased office BP in these patients, 24-hour ambulatory BP remained unchanged (Figure 3).

The ongoing Symplicity HTN-3 trial should provide additional information that may help to clarify discrepancies between office and ambulatory BP measurements.¹⁷

Why Is There a Delayed BP-Lowering Response After RDN?

A progressive increase in the magnitude of the drop in office BP from 1 to 6 months after RDN was reported in the 2 Symplicity trials, and some patients did not show a positive response (≥10 mmHg drop in systolic BP) until ≥6 months after the procedure.^{14–16} However, another study in 46 patients with resistant hypertension reported that both office and ambulatory BP were stable from 1 to 6 months after RDN.³⁸ It may be that follow-up for >6 months is needed to see the maximal response to RDN. With continued follow-up beyond 1 year in Symplicity HTN-1, the average decrease in office BP was 23/11, 26/14, and 32/14 mmHg at 12, 18, and 24 months, respectively.¹⁴ Furthermore, when the follow-up period was extended to 3 years in 44 patients who were nonresponders at 1 month (defined as <10 mmHg drop in systolic BP), the response rate improved to 83% by 3 years (Figure 4).

It is possible that the delayed effect of RDN on BP that has been observed in some studies could be related to a reversal of vascular remodeling. Vascular remodeling in hypertension involves an increase in the wall thickness of arterial resistance vessels with a concomitant reduction in lumen diameter, with

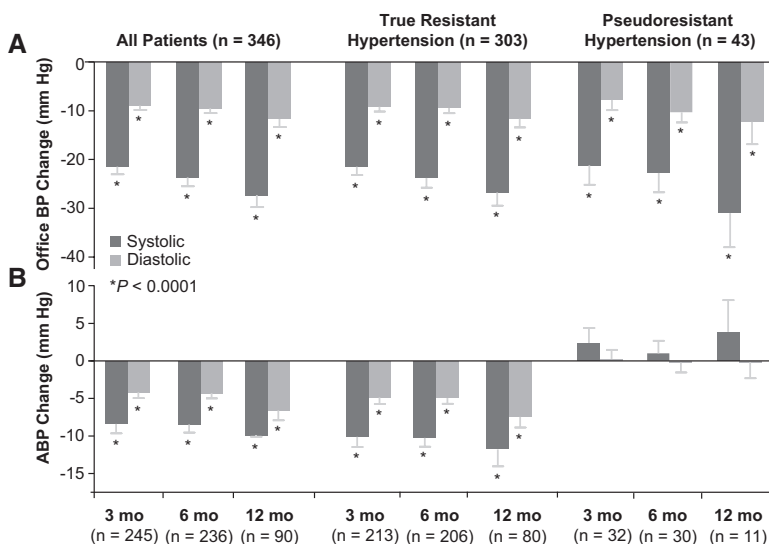


Figure 3. Changes in office (A) and 24-hour ambulatory blood pressure (ABP; B) at 3, 6, and 12 months after renal denervation (RDN) in 346 patients with resistant hypertension. RDN significantly decreased both office and ABP in the entire cohort and in patients with true resistant hypertension (n=303). However, in patients with pseudoresistant hypertension (n=43), RDN decreased only office blood pressure (BP). The data are plotted as mean±SD. All *P* values are for comparison with baseline before RDN. Modified from Mahfoud et al²⁵ with permission of the publisher. Copyright © 2013, American Heart Association, Inc.

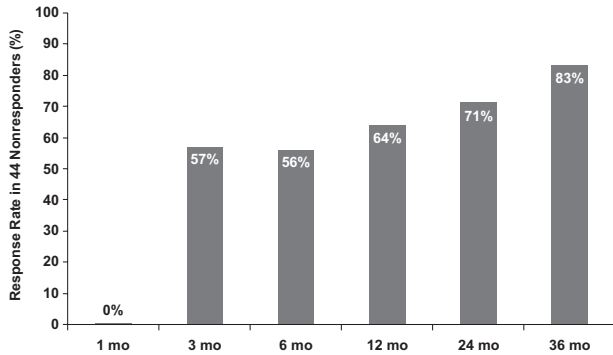


Figure 4. The response rate for 3 years of follow-up in the nonresponders in Symplicity HTN-1. There were 44 patients who were nonresponders at 1 month (defined as <10 mmHg drop in systolic blood pressure), and 83% of these patients responded by 3 years after renal denervation.

the consequence of a further increase in vascular resistance and BP. Because sympathetic tone has been shown to be an important factor in vascular remodeling,⁴¹ a reduction in sympathetic tone after RDN may result in a gradual reversal of vascular remodeling and a delayed decrease in BP. Indirect evidence for a reversal of vascular remodeling after RDN comes from several studies demonstrating a decrease in arterial stiffness and arterial pulse wave velocity 3 to 6 months after RDN.^{42,43}

Alternatively, changes in medication adherence, lifestyle changes, and the use of additional medications after the RDN procedure could also affect the gradual further decrease in BP observed. However, there are several observations that would argue against a major effect of any of these potential factors in the Symplicity studies: (1) the average number of medications taken by participating patients did not change during the course of the studies; (2) although compliance with prescribed medication may improve if a patient is enrolled in a study, compliance tends to get worse over time, which is therefore unlikely to explain further BP drops in the Symplicity studies; (3) although one could argue that compliance may improve after RDN based on the assumption that there is increased awareness of the relevance of BP control after having undergone an interventional procedure for uncontrolled BP, our experience is that patients are perhaps more likely to withdraw medication because they think that the RDN procedure has cured/improved their hypertension, thereby reducing the need for some/all of their medications.

Should Total Denervation be the Goal of Catheter-Based RDN?

At the present time, there is limited information on the extent of efferent or afferent denervation that is achieved by catheter-based RDN. In the initial proof-of-principle cohort, a subgroup of 10 patients whose mean 6-month office BP was reduced by 22/12 mmHg underwent assessment of renal norepinephrine spillover 15 to 30 days after RDN.⁵ Norepinephrine spillover decreased by an average of 47% (95% confidence interval, 28% to 65%), suggesting that there was partial but not total sympathetic efferent denervation. It is possible that more extensive denervation of both the efferent and afferent nerves could result in a greater and more consistent reduction in BP;

however, this may require an increase in the magnitude of RF energy delivered and an increase in the number of renal artery sites ablated. More extensive ablation could increase the risk of renal artery dissection or other adverse events after the procedure.

Based on the available clinical data, there are some patients with resistant hypertension who do not show a reduction in BP in the first 6 months or more after RDN. It is not clear whether there was insufficient denervation or whether the pathophysiology of hypertension is different in these patients. If there was insufficient denervation, then these patients might benefit from a repeat procedure. However, the 36-month follow-up data from Symplicity HTN-1 showed that many of the nonresponders at 1 month became responders between 1 and 3 years (Figure 4).⁴⁴ Thus, it may be better to adopt a wait-and-see approach before a repeat procedure is performed in patients who do not respond in the first 6 months.

Does Reinnervation Occur After RDN?

It is important to consider the role of reinnervation in the long-term effects of RDN on BP and sympathetic tone. A study in normal rats subjected to unilateral surgical RDN showed functional efferent reinnervation of the renal vasculature by 8 weeks after RDN.⁴⁵ In a more recent study in normal rats, immunohistochemistry was used to study both efferent and afferent nerve regeneration after unilateral surgical RDN.⁴⁶ Reinnervation of afferent nerves was found to occur during the same time course as reinnervation of efferent nerves, both being complete by 9 to 12 weeks after RDN.

Currently, there is no functional or anatomic evidence of either efferent or afferent reinnervation after RDN in patients. Although there is histological evidence for regeneration of nerve fibers 8 to 12 months after kidney transplantation in humans,⁴⁷ the transplanted kidney does not show functional efferent reinnervation after either short-term (<2 months) or long-term (>27 months) follow-up.⁴⁸ The durability of the BP responses in Symplicity HTN-1 and HTN-2 suggests that if reinnervation occurred, it did not seem to attenuate or reverse the BP response during 24 to 36 months. If there is complete functional afferent and efferent reinnervation of the kidneys without a reversal of the BP response, then this would suggest that there might be changes in the central nervous system processing of afferent information, which lead to a sustained decrease in sympathetic tone and BP.

Does RDN Have Beneficial Effects Beyond BP Control?

Preliminary and primarily uncontrolled data indicate that RDN may exert additional beneficial effects on the heart, glucose metabolism, health-related quality of life, and others, as briefly described in the online-only Data Supplement B.

Clearly, the data available till date have to be considered hypothesis generating and require confirmation in appropriately designed controlled clinical trials.

Disclosures

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ONLINE DATA SUPPLEMENT:

**Targeting the Sympathetic Nervous System: Critical Issues in Patient Selection,
Efficacy and Safety of Renal Denervation**

Short Title: Efficacy and Safety of Renal Denervation

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A)

A recent consensus statement was developed by the European Society of Cardiology and considers patients eligible for RDN if they meet the following criteria:

- 1) office-based BP >160mmHg (>150mmHg in patients with type 2 diabetes)
- 2) the use of 3 or more antihypertensive drugs in adequate dosages and combinations, including the use of a diuretic (the use of a mineralocorticoid antagonist is optional)
- 3) lifestyle changes to modify BP
- 4) exclusion of secondary hypertension
- 5) exclusion of pseudo-resistant hypertension identified by the use of APBM (average BP >130mmHg or daytime BP >135mmHg), 6) preserved renal function (eGFR >45mL/min/1.73m²)
- 7) no renal artery stenosis >50% or prior renal revascularization
- 8) exclusion of patients with multiple main renal arteries in either kidney or a main renal artery that is <4 mm in diameter or <20 mm in length.³⁵

B)

Does RDN have beneficial effects on the heart?

There is evidence that RDN can improve cardiac function in patients with resistant hypertension. In a sub-study that included 64 patients enrolled in the Symplicity HTN-2 trial, 2-dimensional trans-thoracic echocardiography was performed at 1 and 6 months.¹ Compared with changes from baseline in the control group (n=18), there was a reduction in left ventricular mass and thickness of the inter-ventricular septum at 1 and 6 months in the group with RDN (n=46). This regression in hypertrophy was accompanied by a significant reduction in BP as well as an improvement in left ventricular ejection fraction and diastolic function. RDN has also been reported to have beneficial effects on cardiac rate and rhythm as demonstrated by a reduction in resting heart rate and prolongation of the PR interval after RDN in patients with resistant hypertension.² An anti-arrhythmic effect of RDN in the atria was also suggested from the results of an acute pig study that simulated sleep apnea by transient tracheal occlusion.³ Tracheal occlusion with negative tracheal pressure applied resulted in a shortening of the atrial refractory period and increased the inducibility of AF. RDN attenuated both of these effects and also inhibited the post-apneic rise in BP.

Does RDN affect blood glucose control and insulin sensitivity?

Activation of the sympathetic nervous system is thought to be an important contributor to insulin resistance and the risk of developing type 2 diabetes.⁴ To assess the effect of RDN on glucose control, a pilot study was performed in 50 patients with resistant hypertension.⁵ There were 37 patients that underwent RDN and 13 patients assigned to a control group. In addition to significant reductions in BP at 1 and 3 months, fasting blood glucose and insulin levels were significantly reduced 3 months after RDN. Furthermore, homeostasis model assessment–insulin resistance also decreased at 3 months after RDN, and mean 2-hr glucose levels during oral glucose tolerance testing were significantly reduced. Similar findings were reported from another study that investigated the effects of RDN in 10 patients with obstructive sleep apnea.⁶ In addition to a decrease in the severity of obstructive sleep apnea in the majority of patients, there were significant changes in 2-hr glucose concentrations during oral glucose tolerance testing and

reductions in HbA1c at 6 months after RDN. Although the mechanisms for the lower blood glucose and improved insulin sensitivity after RDN are not clear, a reduction in sympathetic tone is thought to shift blood away from less-sensitive visceral tissue to more insulin-sensitive striated skeletal muscle and to reduce glucagon secretion. Additional studies are needed to define the precise mechanisms by which RDN lowers blood glucose and improves insulin sensitivity in patients with resistant hypertension or other cardiovascular diseases.

Does RDN have an impact on quality of life?

Health-related quality of life (QOL) has been reported to be reduced in many of its domains in patients with hypertension with uncontrolled hypertension having a greater emotional impact on patients than controlled hypertension.⁷ In a cohort of 62 patients QOL assessment was performed before and after RDN.⁸ Before RDN, the 62 patients with resistant and uncontrolled hypertension displayed significantly reduced scores in 5 of the 8 domains in the 36-Item Short-Form Health Survey domains and the Mental Component Summary score, when compared with either a healthy control group or a matched group of patients with pharmacologically controlled hypertension.⁸ After RDN, the Mental Component Summary score improved (47.6 ± 1.1 vs 52 ± 1 ; $p=0.001$) as a result of increases in the vitality, social function, role emotion and mental health domains. The Beck Depression Inventory scores were also improved, particularly with regard to symptoms of sadness, tiredness and libido. RDN was without a detrimental effect on any elements of the 36-Item Short-Form Health Survey. Taken together, these results indicate that patients with severe treatment-resistant hypertension present with a marked reduction in subjective QOL, several aspects of which were improved 3 months after RDN. Interestingly, the improvement in QOL was not directly associated with the magnitude of BP reduction.⁸

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Table S1. Renal function at baseline and 6 and 12 months after RDN in Symplicity HTN-2

Parameter measured at	RDN group	Crossover group
eGFR, mL/min per 1.73 m ²		
Baseline	76.9 ± 19.3 (n=49)	88.8 ± 20.7 (n=35)
6 mo	77.1 ± 18.8 (n=49)	89.3 ± 19.5 (n=35)
12 mo	78.2 ± 17.4 (n=45)	85.2 ± 18.3 (n=35)
Serum creatinine, mg/dL		
Baseline	1.03 ± 0.29 (n=49)	0.84 ± 0.21 (n=35)
6 mo	1.04 ± 0.32 (n=49)	0.83 ± 0.18 (n=35)
12 mo	1.01 ± 0.28 (n=45)	0.86 ± 0.20 (n=35)
Cystatin C, mg/dL		
Baseline	0.91 ± 0.25 (n=38)	0.78 ± 0.17 (n=27)
6 mo	0.98 ± 0.36 (n=40)	0.82 ± 0.16 (n=26)
12 mo	0.98 ± 0.30 (n=38)	0.89 ± 0.20 (n=26)

Patients in the control group were allowed to crossover to RDN after 6 months.

Values are mean ± SD. eGFR, estimated glomerular filtration rate; RDN, renal denervation.