Controversy Over Depressor Effects of Renal Denervation (RDN)

Sympathetic nerve activity (SNA) to the heart, arterioles, and kidneys increases in patients with essential hypertension (HTN), including drug-resistant HTN. In 2009, Esler and colleagues developed and published a dramatic innovation for reducing blood pressure (BP) in drug-resistant HTN patients: RDN. They thermally ablated renal sympathetic nerve fibers through the percutaneous, luminal application of catheter-mediated, radiofrequency energy. RDN was confirmed to reduce norepinephrine content in the kidney of experimental mice. In their pioneering prospective study (Symplicity HTN-1), Esler’s group reported that the office systolic BP decreased by 26 mmHg at 6 months after RDN, but the study did not examine a sham denervation group.

To test whether RDN actually reduces the BP in patients with resistant HTN, Bhatt et al performed a prospective randomized study that included a sham denervation group (SYMPLICITY HTN-3). Although the office BP was reduced at 6 months after RDN, compared with the value before RDN, no significant between-group difference in the change in office BP was seen (−14.1 mmHg in the RDN group vs. −11.7 mmHg in the sham-procedure group). The SYMPLICITY HTN-Japan study subsequently examined changes in office BP of Japanese patients treated with RDN and the BP of those treated with antihypertensive drugs, and did not show a between-group difference of the change in office BP.

Some technical problems were pointed out to explain the lack of a difference in BP between the RDN and sham groups in the SYMPLICITY HTN-3 study. Although at least 4–6 ablations should have been performed for each renal artery, because BP reduction depends on the number of ablation attempts, fewer ablation attempts were performed in some patients. In addition, the denervation should have been applied to the distal segments of the renal arteries, not the proximal segment, because the distance between the endothelium and renal nerve fibers is smaller. If the doctors performing the SYMPLICITY HTN-3 study had followed the procedural protocol, the BP would have been reduced to a
Effects of RDN in HTN Patients With OSA

SNA in patients with OSA is stimulated by hypoxia and/or hypercapnia\(^\text{10}\) (Figure 2). Kario et al had shown that SNA increases in patients with OSA and speculated that RDN might be effective for reducing BP in patients with OSA,\(^\text{11}\) and based on this speculation, they performed an intensive post-hoc analysis of the depressor effects of RDN in a subgroup of patients with OSA who participated in the SYMPLICITY HTN-3 study, which is reported in this issue of the Journal.\(^\text{12}\)

Kario et al demonstrate several important findings. At 6 months after RDN, the change in office systolic BP in the OSA patients was greater in the RDN group than in the sham group, while the change in 24-h ambulatory systolic BP was not significantly different between the 2 treatment groups. In contrast, among the non-OSA patients, there was no difference in either the office or the 24-h ambulatory systolic BP in the RDN and sham groups.

Therefore, RDN was shown to be a really effective and encouraging therapy for reducing BP in a subpopulation of patients with drug-resistant essential HTN.

Interestingly, Kario et al consider one of the mechanisms by which RDN might reduce BP in patients with OSA; namely, RDN might decrease the chronic overload of periharyngeal fluid and alleviate upper airway obstruction.\(^\text{12}\) In other words, RDN might alleviate the actual airway obstruction, resulting in a decrease in the apnea-hypopnea index. In addition, we think that the decrease in peripheral SNA on the heart and arterioles induced by RDN could be another mechanism contributing to BP reduction, because afferent renal nerves stimulate efferent sympathetic nerves, via the hypothalamus, and RDN impairs not only the efferent but also the afferent renal nerves.

Kario et al also found great differences between the RDN and sham treatment groups of OSA patients in peak night-time and maximum night-time systolic BP,\(^\text{12}\) probably because SNA is most strongly stimulated by hypoxia at midnight. Again, these differences between the 2 treatment groups were not observed in the non-OSA subgroup.

Another difficult point to understand is that the improvement in nocturnal BPs in the RDN group was more pronounced in the OSA patients using CPAP/BiPAP than in the OSA patients not using CPAP/BiPAP. Kario et al previously reported that OSA patients using CPAP/BiPAP still experienced a nocturnal BP surge,\(^\text{13}\) suggesting continuation of sympathetic overactivity.

**Issues to Be Resolved in the Near Future**

Some of the difficulties in interpreting the study by Kario et al\(^\text{12}\) can be attributed to the technical problems that influenced the SYMPLICITY HTN-3 study,\(^\text{1,6,8}\) while others may be intrinsic to RDN procedure itself. The following points need to be resolved to improve the rate of successful BP reduction.

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**Figure 2.** Mechanisms by which patients with obstructive sleep apnea (OSA) exhibit increases in sympathetic nerve activity (depicted by Kumagai). Hypoxia induced by OSA stimulates the carotid body (chemoreceptor). Afferent nerves activate the neurons in the rostral ventrolateral medulla (RVLM) area directly and indirectly via the nucleus tractus solitarius (NTS). The activated RVLM neurons increase sympathetic nerve activity to the heart, arterioles, and kidney, elevating blood pressure (BP).
by RDN.

1. Patients with truly drug-resistant HTN should be identified, and patients with white-coat HTN should be excluded.

2. Patients with elevated SNA should be selected. SNA is reflected by the ratio of low-frequency (LF) to high-frequency (HF) bands obtained by spectral analysis of heart rate variability. The exclusion of patients with sodium-dependent HTN is also needed. We have to identify subgroups, such as those with OSA, of patients with essential HTN.

3. A real-time monitoring tool and system should be developed to observe whether sympathetic nerve fibers are actually injured during the RDN procedure. Esler proposed measurement of fragments of urinary tyrosine hydroxylase, a key enzyme involved in catecholamine biosynthesis. We think that the ratio of LF/HF could be a potential real-time marker of changes in SNA.

4. Rules for performing the RDN procedure should be established and strictly followed. The denervation procedure should be performed at the distal segments of each renal artery (Figure 1), and denervation should be done several times on each side of the renal artery. The SYMPLICITY Spyral multielectrode (4 electrodes) RDN catheter has been developed to achieve automated ablation in 4 quadrants of the renal artery circumference. Finally, the quality control of clinical studies should be improved by decreasing the Hawthorne effect and avoiding changes in antihypertensive drugs during the test period.

References


