Editorial

Anticipated expansion of a new approach to treating hypertension without medication by catheter-based renal denervation

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The RADIANCE-HTN SOLO trial recently revealed that catheter-based renal denervation (RDN) using endovascular ultrasound could reduce the ambulatory blood pressure (ABP) after 2 months without medications in patients who had combined systolic/diastolic hypertension (HT) (1). Accordingly, RDN is being re-evaluated because of the contrast to the disappointing results of the SYMPLICITY HTN-3 trial (2), which indicated that RDN did not have an antihypertensive effect.

In fact, detailed analysis of previous trials, including SYMPLICITY HTN-3 (2), suggests that RDN was not actually ineffective. Three main reasons for the unsuccessful outcome of the SYMPLICITY HTN-3 trial have been proposed (3-6).

The first problem was the use of antihypertensive therapy. Because invasive femoral artery puncture is required for RDN, this intervention may have prompted patients to improve adherence to oral antihypertensive therapy in addition to diet. Adherence of patients with treatment-resistant hypertension (R-HT) is usually poor and a method for confirming adherence was not established in the trial. In addition, the baseline period that was set to allow stabilization of the effect of medication was too short. Furthermore, although additional antihypertensive medications should have been avoided according to the original protocol, medications were actually used by many patients. The second reason is related to problems with the RDN device itself and the cauterization strategy. There is no method for objectively confirming whether RDN has been performed adequately, and the proficiency of the operator will influence outcomes. Due to the properties of the device used in SYMPLICITY HTN-3, it is likely that the renal nerves were not completely cauterized to a sufficient depth or around the full circumference of the kidney. The third problem was that many subjects were not appropriate candidates for RDN, including patients with isolated systolic HT and elderly patients who had irreversible elevation of vascular stiffness.

For these reasons, we considered that the outcome of the SYMPLICITY HTN-3 trial reflected deficiencies of the protocol and the catheter technique, while the efficacy of RDN itself was not properly addressed.

Therefore, substantial new trials were designed with more attention to the protocol. In addition to the results of the SPYRAL HTN-ON MED trial (7) in patients with R-HT, the outcomes of the SPYRAL HTN-OFF MED trial (8) and RADIANCE-HTN SOLO trial (1) in patients with mild to moderate HT without oral antihypertensive therapy were all positive for the antihypertensive effect of RDN.

In August 2017, it was reported that RDN reduced BP in the SPYRAL HTN-OFF MED trial using the Symplicity Spyral multi-electrode catheter (8). Thereafter, the results of the SPYRAL HTN-ON MED trial (7) and the RADIANCE-HTN SOLO trial (1) were announced at together in May 2018. It can be considered that the results

of these three clinical trials of RDN have inaugurated a new era in the treatment of HT.

Among these investigations, RADIANCE-HTN SOLO was a multicenter, international, single-blind, randomized, sham-controlled trial. Hypertensive patients were enrolled if their ABP was ≥135/85 and <170/105 mmHg after a 4-week washout period following discontinuation of up to two antihypertensive medications.

The above-mentioned three issues with SYMPLICITY HTN-3 were avoided by the protocol of the RADIANCE-HTN SOLO trial (1). Problems with antihypertensive medication were solved by only enrolling patients who were not on medication. Problems related to the RDN device and cauterization strategy were overcome by using a new generation device that was more effective and reliable. Third, an attempt was made to select patients who were more likely to respond to RDN by restrictions on the enrollment criteria such as tightening the diastolic BP and age.

In the study, a total of 146 patients were randomized to undergo RDN with the Paradise system (ReCor Medical, Palo Alto, CA, USA) (n=74) or a sham procedure (n=72). After follow-up for 2 months, the reduction of daytime systolic ABP was greater with RDN (–8.5 mmHg) than with the sham procedure (–2.2 mmHg) and the baseline-adjusted between-group difference was 6.3 mmHg (P=0.0001). Because some patients were administered antihypertensive medication in the follow-up period after randomization, per-protocol analysis was performed of the off-medication patients (RDN group: n=64; sham group: n=58). The reduction of daytime systolic ABP was significantly larger in the RDN group than in the sham group (by 8.2 mmHg). No major adverse events were reported. Patients in the RDN group received a simple and short procedure, with an average of 5.4 bursts and an average total ablation time of 37.9 sec.

In earlier trials of RDN, poor adherence to scheduled medications and administration of additional drugs were problems that severely compromised assessment of the outcomes, making it difficult to observe the antihypertensive effect of denervation. In the SPYRAL HTN-ON MED trial (7), adherence to medication was evaluated by drug screening and the study was carefully planned, but the adherence rate to oral medication was only 60%. Because there is no need to consider drug adherence in trials of off-medication patients, such studies are important for appropriate examination of the BP-lowering effect of RDN (6). Therefore, the significant BP reduction revealed by two RDN trials targeting off-medication patients has considerable implications for the management of HT.

Among patients with HT, it was reported that about 10% have R-HT (9), while another study using ABP monitoring found a prevalence of 4.1% (10). In contrast, screening of patients to receive RDN found a low prevalence of R-HT, which was around 0.1–0.2% (11).

Current antihypertensive medications are potent, so R-HT is uncommon if patients receive adequate treatment. It seems disappointing that RDN is only being considered for a few patients such as those with R-HT. Instead of limiting RDN to patients with R-HT, introduction of RDN as a treatment option for patients with mild to moderate HT (such as the targets of the off-medication trials) could be much more beneficial. In the real world, many persons have high BP that remains untreated because they do not want to take regular medication, suggesting that offering RDN to patients with mild/moderate HT who wish to avoid medication could have great clinical significance. In addition, adherence to prescribed antihypertensive medications is often poor and treatment is unstable (12,13). Based on the low adherence rate in the SPYRAL HTN-ON MED trial (7), we probably have to accept that adherence to antihypertensive therapy is fundamentally poor. For these reasons, RDN could be very useful as a treatment for HT that avoids the need to take regular medication.

The Paradise system used in the RADIANCE trial was an improvement on the previous generation of RDN systems. It allowed full circumference cauterization to a depth of 1–6 mm from the vessel lumen while cooling the vessel wall tissues with a water-filled balloon inflated at low pressure, suggesting that an antihypertensive effect could be achieved while avoiding damage to the vascular intima (14,15). Cauterization to a depth of 6 mm would be expected to achieve about 80% denervation of efferent and afferent renal sympathetic nerves in the adventitia of the main renal artery (16,17). The safety and efficacy of the Paradise system was confirmed by a prospective, single-group, open-label study in patients with R-HT (18,19).

However, the Paradise system requires a main renal artery diameter (RAD) ≥4 mm (20) due to limitations on the available balloon sizes. Conversely, the Symplicity Spyral catheter used in the SPYRAL HTN trial only requires a RAD >3 mm (21). Generally, the RAD becomes smaller at distal sites, suggesting that the Symplicity Spyral has an advantage over the Paradise system because cauterization of the distal renal artery is more important than proximal cauterization for reducing the BP (17,22). In

addition, cauterizing many points has been recommended for a stronger BP-lowering effect (4). Cauterization was performed at an average of 43.8 points in the SPYRAL HTN OFF-MED (21) versus an average of only 5.4 points in the RADIANCE-HTN SOLO trial (1).

However, procedural time was significantly shorter in the RADIANCE-HTN SOLO trial (cauterization of 5.4 points for 7 seconds each) (21) than in the SPYRAL HTN OFF-MED trial (cauterization of 43.8 points for 60 seconds each) (1), and the reduction of BP was similar despite fewer ablation sites with the Paradise system than the Symplicity Spyral catheter (8). In other words, if the Symplicity Spyral catheter is used to achieve an equivalent reduction of BP to the Paradise system, it requires cauterization at many more sites and the procedure takes far longer. The reason for this difference may be that the endovascular ultrasound catheter delivers energy circumferentially, rather than from individual radiofrequency electrodes. The finding that the number of bursts was not a predictor of the reduction of daytime systolic ABP achieved by the RDN group in the RADIANCE-HTN SOLO trial supports this concept.

Patients who had an accessory renal artery with a diameter ≥2 and <4 mm were excluded from some trials (20) because intact sympathetic nerves around the untreated accessory artery could decrease the effectiveness of RDN. The Symplicity Spyral catheter can cauterize renal arteries with a diameter >3 mm, corresponding to the anatomy of many patients, while the current Paradise system is unable to cauterize renal arteries smaller than 4 mm. About 7% of the patients were excluded from the SPYRAL HTN-OFF MED trial due to anatomical problems. In the RADIANCE-HTN SOLO, a high 14% of patients did not meet the renal anatomical criteria on computed tomography or magnetic resonance imaging and were excluded in the preoperative phase. If renal arteries with a diameter <4 mm could be cauterized by an improved Paradise system in the future, this system with a stronger antihypertensive effect could be employed in many more patients.

In this RADIANCE-HTN SOLO trial, a short follow-up period of 2 months off medication was planned in consideration of patient safety. Since BP reduction by RDN was not significant after 3 months but was significant after 6 months in the SPYRAL HTN-ON MED trial (7), the effect of RDN may change with longer observation. Therefore, the results of RADIANCE-HTN SOLO also require reconsideration after a longer follow-up period. Reduction of the office systolic BP by about 10 mmHg can reduce major cardiovascular events by 20% and mortality by 13% (23). If RDN can maintain a lower BP over the long term, it would be expected to reduce cardiovascular events and improve the vital prognosis.

Since there have been few reports of major adverse events associated with RDN (1,7,8), the safety of this procedure seems to be acceptable. Accordingly, RDN has the potential to become a first-line treatment for HT. In the previous trials, most complications of RDN have been related to the femoral artery access site. Eventually, RDN will become possible via the radial approach, as is the case for percutaneous coronary intervention. In fact, a Paradise system for the radial approach has already been developed, and performing RDN via the radial approach will reduce procedural risks in the future (19). It is considered that percutaneous transluminal renal angioplasty is easier for the operator (and thus safer) via the radial approach than the femoral approach, because the renal artery branches downward and catheter engagement is facilitated. In addition, hemostasis is easy and safe after radial artery puncture. If RDN can be performed via the radial approach, it will become a day procedure rather than requiring overnight hospitalization. In patients with mild HT, minimally invasive RDN could reduce both the cost of long-term medication and the incidence of cardiovascular disease, suggesting that early RDN could contribute to overall reduction of medical costs. The chief concern is the risk of cerebral infarction due to passing the catheter through the subclavian artery. Coronary angiography is often performed via the radial approach nowadays, and cerebral infarction is extremely rare. Therefore, RDN via the radial approach should be tolerable.

It has been suggested that the BP-lowering effect of RDN is too weak. Current catheter-based intervention for coronary artery disease or arrhythmias was not satisfactory at its introduction, but has been improved markedly over time. Likewise, RDN is likely to be improved in the future so that greater reduction of BP is achieved. In addition, the selection of suitable patients for RDN needs more attention. It has been reported that a response to RDN is more likely if patients have the following characteristics: younger age, high baseline BP, obesity, Asian ethnicity, preserved renal function, sleep apnea syndrome, and diastolic HT (1,2,11).

Treatment of HT has entered a new era. Nowadays, invasive treatment for myopia, such as laser-assisted *in situ* keratomileusis (LASIK), is widely accepted in addition to correction of vision with glasses or contact lenses. As with LASIK, RDN will eventually be accepted as first-line therapy for HT by patients who do not want to take

medications indefinitely. We expect that positive results of the RADIANCE-HTN TRIO and REQUIRE trials (20), which are currently in progress, will strengthen the evidence regarding the antihypertensive effect of RDN. Previous studies have suggested that RDN might have pleiotropic beneficial effects on arrhythmias such as atrial fibrillation, as well as improving urinary protein, diabetes, sleep apnea syndrome, congestive heart failure, arteriosclerosis, left ventricular remodeling, depression, quality of life and medical costs. Following the introduction of RDN, current symptomatic treatment for HT will become potentially curative and this will improve the overall prognosis of HT patients.

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Footnote

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