Renal denervation: a new treatment option in resistant arterial hypertension

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Abstract Hypertension is one of the most prevalent cardiovascular risk factors. Despite this high prevalence and a broad availability of effective pharmaceutical agents, a significant proportion of patients do not reach treatment goals. Partly this can be explained by secondary causes of hypertension or non-compliance of patients. Nevertheless, a subgroup of patients can be diagnosed with ‘resistant hypertension’. Activation of the sympathetic nervous system is known to be an important factor in the development and progression of systemic hypertension. In this context, a percutaneous, catheter-based approach has been developed using radiofrequency energy to disrupt renal sympathetic nerves. The first studies have shown this technique to be safe, illustrated by a lack of vascular or renal injury. More importantly, catheter-based renal nerve ablation resulted in a significant reduction in blood pressure on top of traditional medical therapy. Additional to the encouraging effects shown on hypertension, a positive influence of this intervention in other conditions, characterised by sympathetic overactivation, may be expected. Though this technique seems promising, further studies are needed to address long-term safety and efficacy of renal denervation in hypertension and other disease states.

Keywords Renal denervation · Sympathetic nervous system · Resistant hypertension · Sympathetic activity

Hypertension

Hypertension is one of the most prevalent cardiovascular risk factors. Globally, 34 % of adults worldwide have hypertension

and this number is rising.[1, 2] Despite a broad availability of effective pharmaceutical agents, only 32 % of treated men and 37 % of treated women achieve treatment goals.[3] This low success ratio can be caused by non-compliance of patients to medical therapy or secondary causes of hypertension (i.e., primary hyperaldosteronism). However, a subgroup of patients do fulfil the criteria of the phenomenon called ‘resistant hypertension’. In 2008, the American Heart Association (AHA) defined resistant hypertension as a blood pressure (BP) that remains above treatment goals despite the concurrent use of medication from three different antihypertensive classes, including a diuretic, with all agents prescribed at doses that provide optimal benefit.[4] Data indicate that patients with resistant hypertension have an approximately threefold increased risk for adverse cardiovascular outcome compared with patients with well-controlled hypertension.[5] To address problems associated with a rising prevalence of (resistant) hypertension, the sympathetic nervous system (SNS) has gained renewed interest as a therapeutic target.

The sympathetic nervous system

Although the exact pathogenesis of an elevated BP remains unclear, it has become clear that (over)activation of the SNS is an important factor in the development and progression of systemic hypertension.[6] The SNS is known to be responsible for the homeostasis mechanism of multiple organ systems. Anderson et al. measured noradrenalin spillover and muscle sympathetic nerve activity (MSNA) in normotensive and hypertensive subjects.[7] They demonstrated that central sympathetic neural outflow is elevated in subjects with hypertension.[7] Moreover, the degree of SNS (over)activation correlated with the severity of BP elevation.

The response of the kidneys to SNS signalling is one mechanism by which sympathetic activation increases

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BP.[8] Renal sympathetic stimulation promotes renin secretion, reduces urinary sodium excretion, and induces renal vasoconstriction.

The renal sympathetic nervous system comprises both efferent and afferent renal nerves. Efferent renal sympathetic nerves originate from the thoracic and lumbar sympathetic trunk, and terminate in the blood vessels, the juxtaglomerular apparatus, and the renal tubules.[6, 9] When stimulated, these nerves achieve an increased sodium reabsorption, increased renin release leading to antinatriuresis, and a decreased renal blood flow.[10–12]

Communication from the kidneys into the central nervous system drives through the renal afferent nerves. Stimulation of these afferent nerves directly contributes to systemic hypertension.[13] Both the efferent as well as afferent renal sympathetic nerves lie within and immediately adjacent to the wall of the renal artery as recently confirmed in an anatomical study and therefore offer a potential option for treatment.[14]

Denervation of the sympathetic nervous system

The concept of renal denervation, and thereby lowering SNS activity in order to treat hypertension, is not new. Based on the findings that surgical nephrectomy in humans resulted in a reduction of MSNA[15], the concept arose that surgical denervation would be an effective treatment for patients with hypertension. Indeed surgical denervation (e.g., splanchnicectomy) has been shown to be effective in lowering BP.[16] However, these methods were associated with high perioperative morbidity, long-term complications, and even mortality.[17]

In this context, a percutaneous, catheter-based approach has been developed using radiofrequency energy to disrupt renal sympathetic nerves without affecting other abdominal, pelvic, or lower extremity innervations.[18] The catheter is introduced into the renal arteries via femoral access. A bilateral treatment of the renal arteries is performed with the use of radiofrequency (RF) energy delivery. The ablations in the renal artery are conducted in a distal to proximal direction in a circumferentially rotating manner with 5 mm

spacing between each ablation treatment. In preclinical studies this has shown to be effective, reducing norepinephrine levels by 80–90 %, without adverse effects on the vessel wall (Ardian Inc, unpublished).[19]

Clinical studies

The clinical efficacy of percutaneous renal denervation (pRDN) as a treatment strategy for patients with resistant hypertension has been evaluated by the Symplicity HTN-1[18] and HTN-2[20] trials.

In these first studies, pRDN showed to be safe, illustrated by a lack of (long-term) vascular or renal injury. More importantly, catheter-based renal nerve ablation resulted in a significant reduction in both systolic and diastolic BP on top of maximal medical therapy, which has now shown to persist throughout 36 months of follow-up.[21, 22]

Proof of principle, HTN-1

In 2009, Krum et al. performed a multicentre safety and proof-of-principle cohort study to assess safety and BP reduction effectiveness of this new technique.[18] They enrolled 50 patients diagnosed with resistant hypertension, of which 45 underwent pRDN. In treated patients, office systolic/diastolic BP values after bilateral pRDN were reduced by −14/−10, −21/−10, −22/−11, −24/−11, and −27/−17 mmHg at 1, 3, 6, 9, and 12-month follow-up. The effectiveness of pRDN was assessed by noradrenalin spillover in a subgroup of 10 patients, showing a mean reduction in noradrenalin spillover of 47 %. One intraprocedural renal artery dissection occurred before delivery of energy; no other renovascular complications were reported.

In May 2011, the Symplicity HTN-1 Investigators presented data of 24-month follow-up in 18 patients.[21] Two years after pRDN, a mean reduction of 32/14 mmHg in office BP was established. Periprocedural safety was monitored in 153 patients undergoing pRDN. In this population, 3 groin pseudoaneurysms and 1 renal artery dissection were noted.

Table 1 Results of different devices for pRDN

Supplier	Brand name	Technology	1 month FU	3 months FU	6 months FU
Medtronic	Symplicity®	RF	N=138 SBP ↓20 mmHg◇	N=135 SBP ↓24 mmHg◇	N=86 SBP ↓25 mmHg◇
Covidien	One shot™	RF	N=10 SBP ↓31 mmHg*		
St. Jude	EnligHTN™	RF	N=62 SBP ↓28 mmHg*	N=46 SBP ↓27 mmHg†	
Vessix Vascular	V2 RF balloon	RF	N=10 SBP ↓30 mmHg*		
Recor Medical	PARADISE™	Ultrasound based	N=10 SBP ↓31 mmHg‡	N=15 SBP ↓32 mmHg*	N=8 SBP ↓33 mmHg†

FU follow-up, RF radiofrequency, SBP systolic blood pressure

‡ Presented at TRenD 2012, Frankfurt; * presented at EuroPCR 2012, Paris; † Presented at ESC Congress 2012, Munich; ◇ Symplicity HTN-1

Randomised controlled, HTN-2

To confirm the findings of the proof-of-principle study, the randomised controlled Symplicity HTN-2 trial was conducted. In this trial, 106 patients were randomly allocated in a one-to-one ratio to undergo renal denervation with previous denervation ($n=52$) or to maintain previous treatment alone (control group, $n=54$). After 6-month follow-up, office BP decreased by 32/12 mmHg ($P<0.0001$), whereas the BP did not differ in the control group. Home and ambulatory BP followed a similar pattern; reductions were 20/12 mmHg and 11/7 mmHg respectively with pRDN, while no reductions were observed in the control group. Although the investigators noted no substantial adverse events, the trial had several limitations (no sham, no exclusion of white coat hypertension). Furthermore, a small subgroup of patients ($n=5$) did not respond to treatment. This indicates a limitation of current devices for pRDN; they lack periprocedural markers to identify whether a patient will respond to treatment.

In addition to the positive effect of renal denervation in BP reduction, pRDN may also have a positive effect on other conditions characterised by sympathetic overactivity. This includes heart failure, sleep apnoea, insulin resistance and even metabolic changes in polycystic ovary syndrome.[23–27] Obviously, these preliminary results have to be confirmed in larger prospective controlled trials.

Results of pRDN in daily practice

The BP-lowering effect of pRDN has not only been studied in the setting of the HTN trials. Different centres have published their first clinical experiences of this promising treatment modality.[19, 28–32] These analyses show a similar reduction in office BP as reported in the first clinical trials. However, the effect of pRDN on ambulatory BP measurements (ABPM) differed throughout the studies. In most reports, the same catheters were used as during the HTN trials. Prochnau et al., however, used a standard electrophysiology catheter.[33] With this catheter, a similar reduction of 24/14 mmHg in ABPM after 3-month follow-up could be achieved.

Given the promising effects of this new treatment modality, many other alternative catheter systems using high frequency ultrasound or using multiple electrodes for RF energy delivery have been presented at recent meetings showing similar preliminary first results (Table 1).[34–36]

Conclusion

Renal denervation is a promising novel treatment option for (resistant) hypertension and potentially other conditions

which are affected by sympathetic overactivity. Currently, different devices to lower sympathetic activity have been developed. Future studies of these new devices, their long-term effects, safety, and the effects on other conditions than hypertension have to be awaited.

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