



REVIEW ARTICLE

Renal denervation in the treatment of resistant hypertension: Dead, alive or surviving?



Ahmad Al-Fakhouri^{a,*}, Nephertiti Efeovbokhan^b, Rami Nakhla^c, Rami N. Khouzam^b

^a Department of Medicine, Methodist South Hospital, Memphis, TN, United States

^b Department of Medicine, Division of Cardiovascular Diseases, University of Tennessee Health Science Center, Memphis, TN, United States

^c Ain Shams University School of Medicine, Cairo, Egypt

Received 26 December 2015; accepted 6 June 2016

KEYWORDS

Hypertension;
Resistant hypertension;
Renal denervation;
Sympathetic nervous system

Abstract Hypertension is one of the most common chronic clinical problems encountered by physicians. The prevalence of resistant hypertension is estimated at 9% in the US. Patients with resistant hypertension have been shown to be at higher risk for adverse cardiovascular events, hence the need for greater efforts in improving the treatment of hypertension. The renal sympathetic nerves play an important role in the development of hypertension, mediated via sodium and water retention, increased renin release and alterations in renal blood flow. The proximity of the afferent and efferent renal sympathetic nerves to the adventitia of the renal arteries suggested the feasibility of an endovascular, selective, minimally invasive approach to renal denervation; a potential treatment option for resistant hypertension. While the RAPID, Reduce-HTN, EnligHTN, DENERHTN and Symplicity HTN-1 and -2 studies showed significant benefit of renal denervation in the treatment of resistant hypertension, the results of Oslo RDN, Prague-15 and Symplicity HTN-3 were not so favorable. Future well-designed clinical trials are needed to ascertain the benefits or otherwise of renal denervation in treatment-resistant hypertension. © 2016 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. All rights reserved.

PALAVRAS-CHAVE

Hipertensão;
Hipertensão arterial resistente;
Desnervação renal;
Sistema nervoso simpático

Desnervação renal no tratamento da hipertensão arterial resistente: morta, viva ou sobrevivendo?

Resumo A hipertensão arterial é um dos problemas clínicos crónicos mais frequentes. Nos EUA a prevalência de hipertensão arterial resistente está estimada em 9%. Os doentes com hipertensão resistente têm um maior risco de eventos cardiovasculares adversos, o que justifica maiores esforços na melhoria do tratamento da hipertensão. A inervação simpática renal tem um papel

* Corresponding author.

E-mail address: fakhouri_md@yahoo.com (A. Al-Fakhouri).

importante no desenvolvimento da hipertensão, mediada através da retenção de sódio e água, com aumento da libertação de renina e de alterações do fluxo sanguíneo renal. A anatomia da inervação simpática renal, com os seus nervos aferentes e eferentes em relação de proximidade com a adventícia, permite uma abordagem endovascular, seletiva e minimamente invasiva para a desnervação renal, e constitui uma opção de tratamento potencial para a hipertensão arterial resistente. Enquanto os estudos RAPID, *Reduce-HTN*, EngliHTN, DENERHTN e *Simplicity HTN* 1,2 mostraram um benefício significativo da desnervação renal no tratamento da hipertensão arterial resistente, os resultados dos estudos Oslo-RDN, *Prague-15* e *Simplicity HTN* 3 não foram tão favoráveis. Serão necessários ensaios clínicos bem estruturados para confirmar ou infirmar os potenciais benefícios da desnervação renal no tratamento da hipertensão arterial resistente. © 2016 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L.U. Todos os direitos reservados.

Introduction

Hypertension is one of the most common chronic clinical problems encountered by physicians. Resistant hypertension is defined as systolic blood pressure (BP) ≥ 160 mmHg or (≥ 150 mmHg in patients with type 2 diabetes mellitus) refractory to medical treatment despite the use of optimal doses of three or more different drug types including a diuretic.¹ The prevalence of resistant hypertension is estimated at 9% in the US.² In a study of 205 750 treated hypertensive patients, 1 in 50 developed resistant hypertension within a median of 1.5 years from the initial treatment.³ In the same study, patients with resistant hypertension were shown to be at higher risk for adverse cardiovascular events.³ The increased morbidity and mortality associated with this condition supports greater efforts to improve treatment options.

Historical perspective

After a link was established between the sympathetic nervous system and the development of resistant hypertension, surgical sympathectomy was introduced in the 1930s, but was abandoned shortly afterwards due to multiple side effects such as postural hypotension, tachycardia, bladder, bowel and erectile dysfunction, and high periprocedural mortality.⁴ The proximity of the afferent and efferent renal sympathetic nerves to the adventitia of the renal arteries suggested the feasibility of an endovascular, selective, minimally invasive approach to renal denervation (RDN). In the endovascular approach, a treatment catheter is introduced through a guiding catheter into the renal arteries. The catheter is placed in close proximity to the vessel wall to ensure stable contact. Low-energy radiofrequency ablations are then applied moving the catheter from distal to proximal locations in the renal arteries.⁵

Anatomical and physiological effects of renal denervation

The renal nerves arise from T10-L2 and follow the course of the renal artery lying in the adventitia. Renal sympathetic

nerves play an important role in the development of hypertension, mediated via sodium and water retention, increased renin release, and alterations in renal blood flow.⁵

Experimental studies established the important concept that sub-vasoconstrictor levels of renal sympathetic activity can increase renin secretion and renal sodium retention without changing renal hemodynamics.⁶ Assessment of regional overflow of norepinephrine (NE) from the kidneys to plasma has demonstrated that renal NE spillover rates can be markedly elevated in patients with essential hypertension and are associated with hypertensive end-organ damage.^{5,31} Measurement of NE excretion in the urine, now largely obsolete, was performed in order to quantify sympathetic nervous system activity in humans.⁶ In the light of these findings, RDN therapy was considered a logical therapeutic approach in the treatment of hypertension.

The sympathetic nervous system and cardiovascular disease⁷

Surgical sympathectomy was first introduced in the 1930s and was effective in lowering high BP in patients with severe hypertension.^{8,9} However, the side effects associated with the procedure and the introduction of ganglionic blockers made it obsolete.¹⁰ For a long time, it was difficult to study and assess the role of the sympathetic nervous system (SNS) in the pathogenesis of hypertension, due not to uncertainty concerning the relation between the two, but rather to the difficulty of testing and assessing that relation. Previous techniques included the measurement of serum and urinary excretion of NE and its derivatives, yielding a rough estimate of SNS activity in the whole body.¹¹ Hagbarth and Vallbo reported microneurography as a newer tool to study SNS nerve firing in subcutaneous tissues and skeletal muscles.¹² The NE spillover technique was first used by Esler et al.,¹³ measuring organ-specific NE release in its efferent veins as an indirect measurement of SNS nerve fiber firing in an individual organ,¹⁴ and that technique was later used to demonstrate that heart failure caused SNS overactivity.¹⁵ Accumulated evidence underlines the role of sustained chronic SNS activity in many diseases including ischemic heart disease,¹⁶ heart failure,^{17,18} hypertension,^{19–21} kidney disease,²² type

2 diabetes,²³ obesity,²³ metabolic syndrome,²³ obstructive sleep apnea,²⁴ depression,²⁵ and inflammatory bowel disease.²⁶

In the cardiovascular system, chronic SNS activation not only raises BP but also causes hypertrophy and proliferation of vascular smooth muscle cells and cardiac myocytes, thus increasing LV mass and wall thickness.²⁷ In addition, increased SNS activity, in the presence of endothelial dysfunction and endothelial cell damage, has been shown to contribute to the development of atherosclerosis.^{25,27,29} Contradicting previous assumptions, high levels of NE spillover from the heart in heart failure²⁸ demonstrated increased sympathetic activity in the failing heart, which was the rationale for the subsequent use of beta-blockers in heart failure.²⁹ In essential hypertension, SNS outflow to the kidneys is elevated and is directly proportional to the severity of hypertension.^{19,21,25} This finding is also supported by regional measurements of NE spillover to the kidneys.³⁰ Renal sympathetic activity is a major factor contributing to the pathogenesis of essential hypertension through its influence on activation of the renin-angiotensin system, sodium and water excretion, peripheral vasoconstriction, cardiac contraction, and venous capacitance.²⁵ The recent introduction of safe and efficient methods for RDN has led to a renewed interest in the role of SNS activation in essential hypertension.

Evidence of the efficacy of renal denervation in the treatment of resistant hypertension

The Rapid Renal Sympathetic Denervation for Resistant Hypertension Using the OneShot™ Ablation System (RAPID) study³² was a prospective, multicenter, non-randomized, single-arm trial that included 50 patients with mean office BP of $181 \pm 20.8/95 \pm 15.5$ mmHg, on a mean of five antihypertensive medications, who received RDN. The primary endpoint studied was the rate of office systolic BP (SBP) reduction: ≥ 10 mmHg at six months in comparison to baseline. Change in 24-hour ambulatory BP (ABP) was also evaluated. At the six-month mark, there was a decrease in mean office BP of $-20/-8$ mmHg ($p < 0.0001/p = 0.0002$) in comparison to baseline. This trend was sustained at 12 months, with a decrease in mean office BP of $-22/-8$ mmHg ($p < 0.0001/p = 0.0014$). Likewise, there was a significant reduction in 24-hour ABP, of $-11/-6$ mmHg at six months in comparison to baseline ($p = 0.0085/p = 0.037$). At 12 months, the reduction in 24-hour ABP was $-9/-5$ mmHg ($p = 0.054/p = 0.073$). Device- and/or procedure-related adverse effects occurred in three patients up to 12 months, namely one access site infection, one renal artery stenosis, and one groin paresthesia. The authors concluded that RDN led to significant and sustained reductions in office and 24-hour ambulatory BP at six and 12 months, respectively.

The REDUCE-HTN study³³ was a prospective, non-randomized, single-arm trial that included 146 patients with mean baseline office and ambulatory BP of $182 \pm 18.4/100 \pm 14.0$ and $153 \pm 15.1/87 \pm 13.2$ mmHg, respectively, who received RDN using the Vessix renal denervation system. The primary efficacy endpoints were reductions in office and 24-hour ambulatory SBP and diastolic blood

pressure (DBP) at six months, which were $24.7 \pm 22.1/10.3 \pm 12.7$ mmHg ($p < 0.0001$) and $8.4 \pm 14.4/5.9 \pm 9.1$ mmHg ($p < 0.0001$), respectively. Regarding the safety endpoints, no acute renal injury requiring acute renal intervention occurred and only one patient developed renal artery stenosis that required a stent. In addition, mean glomerular filtration rate remained stable. The authors concluded that renal artery denervation reduced both office and ambulatory BP at six months in patients with resistant hypertension.

The EnlighTN I study³⁴ was a prospective, non-randomized trial that included 46 patients with mean baseline office, 24-hour ambulatory and home BP of $176/96$, $150/83$ and $158/90$ mmHg, respectively, who underwent RDN using the EnlighTN multielectrode radiofrequency ablation system. The primary efficacy endpoint was change in office BP in comparison to baseline. The mean reductions in office BP at 1, 3, 6, and 12 months were $-28/-10$, $-27/-10$, $-26/-10$, and $-27/-11$ mmHg, respectively ($p < 0.001$ for all). Likewise, mean reductions in 24-hour ABP were $-10/-5$, $-10/-5$, and $-10/-6$ mmHg at 1, 3, 6 months ($p < 0.001$ for all), and $-7/-4$ mmHg at 12 months ($p < 0.0094$). Mean reductions in home measurements were $-9/-4$, $-8/-5$, $-10/-7$, and $-11/-6$ mmHg ($p < 0.001$ at 12 months). There were no signs of worsening renal function at 12 months. One patient required renal artery stenting (non-occlusive renal stenosis was present at baseline). The authors concluded that the EnlighTN ablation system was safe and effective in reducing office, 24-ambulatory and home BP in patients with resistant hypertension.

Oslo RDN³⁵ was a prospective randomized trial in which 19 patients with true treatment-resistant hypertension were randomized to RDN ($n=9$) performed with the Symplicity Catheter System vs. clinically adjusted drug treatment ($n=10$). True treatment-resistant hypertension was confirmed after excluding patients with confounding poor drug adherence. The primary endpoint was change in office systolic blood pressure (SBP) from randomization to six months. The study was stopped early as RDN had uncertain BP-lowering effects. At six months, office SBP and DBP changed significantly from $160 \pm 14/88 \pm 13$ mmHg to $132 \pm 10/77 \pm 8$ mmHg compared to baseline in the drug-adjusted group ($p < 0.0005$ and $p = 0.02$), whereas in the RDN group there was no significant change in office SBP and DBP at six months compared to baseline ($156 \pm 13/91 \pm 15$ to $148 \pm 7/89 \pm 8$ mmHg, $p = 0.42$ and $p = 0.48$). SBP and DBP were significantly lower in the drug-adjusted group at six months ($p = 0.002$ and $p = 0.004$, respectively), and absolute changes in SBP were larger in the drug-adjusted group ($p = 0.008$). ABP changed in parallel to office BP. The authors concluded that the BP-lowering effect of adjusted drug treatment were superior to that of RDN in patients with true treatment-resistant hypertension.

The Prague-15 study³⁶ was a prospective, open-label multicenter trial in which 106 patients with resistant hypertension were randomized to RDN ($n=52$) or intensified pharmacological treatment ($n=54$). RDN was performed using the Symplicity Renal Denervation System. At six months, a comparable significant reduction in mean 24-hour SBP was noted in both groups, of -8.6 mmHg (95% confidence interval [CI]: -11.8 , -5.3); $p < 0.001$ in RDN, vs. -8.1 (95% CI: -12.7 , -3.4) mmHg in the pharmacological group. Likewise,

a significant reduction in office SBP was observed in both groups mmHg (-12.4 [95% CI: -17.0, -7.8]; $p < 0.001$ in RDN vs. -14.3 mmHg [95% CI: -19.7, -8.9]; $p < 0.001$ in the pharmacological group). The authors concluded that RDN was safe; however in the setting of true resistant hypertension with confirmed compliance, it was not proved superior to intensified pharmacological treatment.

The DENERHTN trial³⁷ was a prospective, open-label randomized controlled trial that assigned 106 patients to receive either RDN plus a standardized stepped-care antihypertensive treatment (SSAHT) regimen (RDN group, $n=53$) or SSAHT alone (control group, $n=53$). Prior to randomization, treatment resistance was confirmed by ABP monitoring after patients received oral antihypertensives for a period of four weeks. The primary endpoint studied was the mean change in daytime SBP from baseline to six months as assessed by ambulatory BP monitoring. The safety outcomes were the incidence of acute adverse events of the RDN procedure and the change in estimated glomerular filtration rate from baseline to six months. At six months, the mean change in daytime ambulatory SBP was -15.8 mmHg (95% CI -19.7 to -11.9) in the RDN group and -9.9 mmHg (-13.6 to -6.2) in the group receiving SSAHT alone, a baseline-adjusted difference of -5.9 mmHg (-11.3 to -0.5; $p=0.0329$). The numbers of antihypertensive drugs and drug adherence at six months were similar between the two groups. Three minor RDN-related adverse events were noted (lumbar pain in two patients and mild groin hematoma in one patient). The authors concluded that RDN plus SSAHT decreases ambulatory BP more than the same SSAHT alone at six months in patients with well-defined resistant hypertension.

The Symplicity HTN studies

The Symplicity HTN-1 study³⁸ was a proof-of-principle trial of therapeutic renal sympathetic denervation. The trial included 50 patients with resistant hypertension who received percutaneous radiofrequency catheter-based RDN using the Symplicity catheter, with a one-year follow-up post procedure. The primary endpoints were office BP and safety data before and at 1, 3, 6, 9, and 12 months after procedure. Out of the 50 patients enrolled, five were excluded for anatomical reasons. Treated patients were on a mean of 4.7 antihypertensive medications, with baseline mean office BP of 177/101 mmHg. Office BP readings after the procedure were reduced by -14/-10, -21/-10, -22/-11, -24/-11, and -27/-17 mmHg at 1, 3, 6, 9, and 12 months, respectively. In the five non-treated patients, mean rise in office BP was +3/-2, +2/+3, +14/+9, and +26/+17 mmHg at 1, 3, 6, and 9 months, respectively. The only reported complication was one intraprocedural renal artery dissection which occurred before radiofrequency energy delivery. The authors concluded that catheter-based RDN leads to substantial and sustained BP reduction, without serious adverse events, in patients with resistant hypertension.

Following the success achieved in the Symplicity HTN-1 trial, the Symplicity HTN-2 trial³⁹ was designed to assess the effectiveness and safety of catheter-based RDN for BP reduction in patients with treatment-resistant hypertension. A total of 106 patients with resistant hypertension were randomly assigned to either RDN with medical treatment

(treatment arm, $n=52$) or medical treatment alone (control arm, $n=54$). The primary endpoint of the study was change in office-based measurement of SBP at six months. At six months, there was a significant reduction in office-based BP measurements in the treatment arm (change of 32/12 mmHg, standard deviation [SD] 23/11, baseline of 178/96 mmHg), compared to the control arm (change of 1/0 mmHg, SD 21/10, baseline of 178/97 mmHg). Between-group differences in BP at six months were 33/11 mmHg ($p < 0.0001$). Additionally, at six months, 41 (84%) out of 49 patients in the treatment arm had a reduction in SBP of 10 mmHg or more, compared with 18 (35%) of 51 controls ($p < 0.0001$). No serious procedural complications were noted. The authors concluded that catheter-based RDN can safely be used to substantially reduce BP in treatment-resistant hypertensive patients. Follow-up at 36 months in 40 of the 52 patients in the initial RDN group and at 30 months in 30 of 37 patients who crossed over and received RDN at six months⁴⁰ showed that SBP decreased by 34 mmHg (95% CI: -40, -27, $p < 0.01$) and DBP decreased by 13 mmHg (95% CI: -16, -10, $p < 0.01$) from a baseline of $184 \pm 19/99 \pm 16$ mmHg. SBP and DBP reductions at 36 months for the initial RDN group was -33 mmHg (95% CI: -40, -25, $p < 0.01$) and -14 mmHg (95% CI: -17, -10, $p < 0.01$), respectively.

In an attempt to further explore the robustness of RDN in the treatment of resistant hypertension, the Symplicity HTN-3 trial⁴¹ was conducted. Unlike the previous two studies, blinding and sham-control were added in the design of this trial. A total of 535 patients with severe resistant hypertension receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs including a diuretic were randomly assigned in a 2:1 ratio to undergo RDN ($n=364$) or a sham procedure ($n=171$).

The primary efficacy endpoint, change in office SBP at six months, was not significantly different between the two groups (-14.13 \pm 23.93 mmHg in the denervation group compared to -11.74 \pm 25.94 mmHg in the sham-procedure group [$p < 0.001$ for both comparisons of the change from baseline], a difference of -2.39 mmHg [95% CI: -6.89 to 2.12; $p=0.26$ for superiority with a margin of 5 mm Hg]). Likewise, for the secondary efficacy endpoint, the change in mean 24-hour ambulatory SBP, no between-group differences were noted -6.75 \pm 15.11 mmHg in the denervation group and -4.79 \pm 17.25 mmHg in the sham-procedure group, for a difference of -1.96 mmHg (95% CI: -4.97 to 1.06; $p=0.98$ for superiority with a margin of 2 mmHg). The primary safety endpoint (a composite of death, end-stage renal disease, an embolic event resulting in end-organ damage, renovascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within six months) was not significantly different between the two groups. The authors concluded that their blinded trial did not show a significant reduction of SBP in patients with resistant hypertension six months after renal-artery denervation compared with a sham control.

Table 1 shows a summary of trials of RDN.

Discussion

The role of RDN in the treatment of resistant hypertension is still to be fully clarified. While the results of the RAPID,

Table 1 Summary of trials of renal denervation.

Trial name/year of publication	Study design	Baseline office and ambulatory BP (mmHg)	Mean no. of AH drugs	% of patients under aldosterone antagonists	Ablation catheter	Study description	Study endpoints	Main findings
RAPID/2014 ³²	Prospective, multicenter, single arm	Baseline office 181.6±20.8/95.5±15.5	5.1	N/A	OneShot™ RF balloon catheter	50 patients enrolled to receive percutaneous RF renal nerve ablation.	Primary endpoint: rate of office SBP reduction ≥10 mmHg at 6 months in comparison to baseline. Change in 24-hour ambulatory BP was also evaluated.	Significant reduction in office and ambulatory BP
REDUCE-HTN/2014 ³³	Prospective, non-randomized, single arm	Baseline office 182±18.4/100±14.0; baseline ambulatory 153±15.1/87±13.2	>3	N/A	Vessix RF catheter (Boston Scientific) Bipolar RF	146 patients enrolled to receive percutaneous RF renal nerve ablation	Primary efficacy endpoints: reductions in office and 24-hour ambulatory SBP and DBP at six months. Acute and long-term safety, with a focus on the renal artery and eGFR	Significant reduction in office and ambulatory BP
EnligHTN/2014 ³⁴	Prospective, non-randomized	Baseline office 176/96; baseline ambulatory 150/83	4.7±1.0	6%	EnligHTN multielectrode RF catheter (St. Jude Medical)	46 patients enrolled to receive percutaneous RF renal nerve ablation using a multielectrode system	Primary efficacy endpoint: office BP change from baseline. Primary safety objective: the rate of adverse events.	Significant reductions in office, ambulatory and home BP
Oslo RDN/2014 ³⁵	Prospective, randomized	Baseline office 156/91; baseline ambulatory 152/93	5.1	3%	Symlicity single-electrode RF catheter	19 patients randomly assigned to RDN (9) or clinically adjusted drug treatment (10)	Primary end-point: change in office SBP from randomization to 6 months	Significant reduction in office SBP in patients assigned to clinically adjusted drug treatment; no change in those assigned to RDN

Table 1 (Continued)

Trial name/year of publication	Study design	Baseline office and ambulatory BP (mmHg)	Mean no. of AH drugs	% of patients under aldosterone antagonists	Ablation catheter	Study description	Study endpoints	Main findings
Prague-15/2015 ³⁶	Prospective, randomized	Baseline office 159±19/92±14; baseline ambulatory 149±12/86±10	5.1±1.2	27%	Symlicity single-electrode RF catheter	106 patients randomly assigned to RDN (52) or intensified pharmacotherapy (54)	Efficacy of RDN assessed by 24-hour ABPM and office BP at 6 months	Significant reduction in 24-hour ambulatory and office BP in both groups, with no differences between groups
DENERHTN/2015 ³⁷	Prospective, randomized	N/A	N/A	N/A	Symlicity RF catheter (Medtronic)	106 patients randomly assigned to RDN + SSAHT (53) or SSAHT alone (53)	Primary end-point: change in daytime SBP assessed by ambulatory BPM	Significant reduction in daytime SBP in patients assigned to RDN + SSAHT as compared to SSAHT alone
Symlicity HTN-1/2009 ³⁸	Prospective, non-randomized	Baseline office 177/101 (SD 20/15)	4.7	N/A	Symlicity single-electrode RF catheter	50 patients enrolled to receive percutaneous RF renal nerve ablation	Primary endpoint: change in office BP at 1, 3, 6, 9, and 12 months after procedure	Significant reduction in office BP
Symlicity HTN-2/2010 ^{39,40}	Prospective, randomized	Baseline office 178±18/97±16	5.1±1.4	19%	Symlicity single-electrode RF catheter	106 patients randomly assigned to RDN (52) or medical treatment (54)	Primary endpoint: change in office-based measurement of SBP at 6 months	Significant reduction in office BP in patients treated with RDN compared with those treated with medical therapy
Symlicity HTN-3/2014 ⁴¹	Prospective, randomized, blinded, sham-controlled	N/A	5.1±1.4	22.5%	Symlicity single-electrode RF catheter	535 patients randomly assigned to undergo RDN (364) or sham procedure (171)	Primary endpoint: change in office BP at 6 months	No significant difference in office BP between the two groups

ABPM: ambulatory blood pressure monitoring; AH: antihypertensive; BP: blood pressure; eGFR: estimated glomerular filtration rate; N/A: not applicable; RDN: renal denervation; RF: radiofrequency; SSAHT: standardized stepped-care antihypertensive treatment; SD: standard deviation.

REDUCE-HTN, EnligHTN, Symplicity HTN-1 and -2, and DENERHTN trials were positive, this was not the case in the Oslo RDN, Prague-15 and Symplicity HTN-3 trials. The varying results may be explained by several factors. Symplicity HTN-3, the largest trial to date, was also the only one that included a sham-control group. As shown by Meissner et al.,⁴⁶ sham procedures may be associated with a significant positive response – the placebo effect – that could be misinterpreted as a real treatment effect. Kandzari et al.⁴² investigated potential reasons for the discordant results noted in Symplicity HTN-3. Their findings showed that between randomization and the six-month endpoint, 39% of patients underwent medication changes involving alteration in both the dose and class of prescribed medications. In addition, African-Americans were more likely to be prescribed vasodilators than non-African-Americans in both study arms. A total of 56% of African-American sham patients and 46.7% of African-American RDN patients were receiving a vasodilator, compared to 40.5% of non-African-American sham control patients and 33.7% of non-African-American RDN patients who were receiving a vasodilator at baseline. African-Americans in the sham control study arm receiving a vasodilator showed an enormous decline in SBP (-21.9+29.1 mmHg), which was not noted in the other subgroups. This unexpectedly large SBP decline in African-American control patients may indicate a change in medical adherence or type of therapy in this specific group. Likewise, increasing number of ablations and energy delivery in a four-quadrant pattern was associated with greater reductions in office and ambulatory SBP and heart rate.

The ablation catheters used in the above studies had some design features that are worthy of mention. The EnligHTN denervation system is a unique multielectrode catheter that allows a predictable pattern of four simultaneous ablations. The Vessix denervation system used in the REDUCE-HTN trial delivered bipolar radiofrequency energy as opposed to the monopolar radiofrequency energy delivered by the Symplicity denervation system (used in the Symplicity HTN studies). As suggested by Kandzari et al.,⁴² differences in ablation energy may affect the efficacy of denervation therapy.

The future

Several trials are underway to investigate the role of RDN in specific patient populations such as those with chronic renal disease and moderate hypertension.^{43–45}

The SPYRAL HTN Global Clinical Trial Program⁴⁷ is a phased series of clinical trials designed to establish the efficacy of RDN therapy in patients with hypertension. The SPYRAL HTN-OFF MED trial aims to confirm the basic hypothesis that RDN therapy lowers BP in patients with hypertension without treatment, while the parallel SPYRAL HTN-ON MED trial is designed to assess the efficacy of RDN integrated with antihypertensive medications.

Conclusions

The results of the RAPID, REDUCE-HTN, EnligHTN, Symplicity HTN-1 and -2, and DENERHTN trials suggested an important

role for RDN in the treatment of resistant hypertension. The results of the Oslo RDN, Prague-15 and Symplicity HTN-3 suggested differently. Of note, all these studies showing favorable benefits of RDN were either non-randomized single-arm trials or randomized unblinded trials without a sham control group. As shown by Meissner et al.,⁴⁶ sham procedures may be associated with a significant positive response – the placebo effect – that could be misinterpreted as a real treatment effect. Symplicity HTN-3, a well-designed randomized, blinded, sham control trial, casts doubt on the benefits of RDN in the treatment of resistant hypertension. The results of the Symplicity HTN-3 emphasize the need always to assess for a potential placebo effect by including sham control study groups when assessing the efficacy of new devices. In addition, future studies should ensure consistent medical therapy and delivery of radiofrequency ablation across treatment arms, as post-hoc analysis showed these differences to be important in the neutral results noted in Symplicity HTN-3.

Currently, the role of RDN in addition to medical therapy in the treatment of resistant hypertension is still to be fully clarified. Nevertheless, RDN is certainly not dead, but further well-designed clinical trials are needed to ascertain the benefits or otherwise of RDN in treatment-resistant hypertension.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2007;25:1105–87.
2. Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. *Hypertension.* 2011;57:1076–80.
3. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation.* 2012;125:1635–42.
4. Morrissey DM, Brookes VS, Cooke WT. Sympathectomy in the treatment of hypertension: review of 122 cases. *Lancet.* 1953;1:403–8.
5. Schlaich MP, Schmieder RE, Bakris G, et al. International expert consensus statement: percutaneous transluminal renal denervation for the treatment of resistant hypertension. *J Am Coll Cardiol.* 2013;62:2031–45.
6. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J.* 2012;33:1058–66.
7. de Sousa Almeida M, de Araújo Gonçalves P, Infante de Oliveira E, et al. Renal denervation for resistant hypertension. *Rev Port Cardiol.* 2015;34:125–35.
8. Hoobler SW, Manning JT, Paine WG, et al. The effects of splanchnicectomy on the blood pressure in hypertension; a controlled study. *Circulation.* 1951;4:173–83.
9. Smithwick RH, Whitelaw GP, Kinsey D. Surgical approach to the treatment of essential hypertension. Results of therapy (medical and surgical). *Am J Cardiol.* 1962;9:893–9.
10. Harington M, Kincaid-Smith P, McMichael MJ. Results of treatment in malignant hypertension: a seven-year experience in 94 cases. *Br Med J.* 1959;2:969–80.

11. Von Euler US, Hellner S, Purkhold A. Excretion of noradrenaline in urine in hypertension. *Scand J Clin Lab Invest.* 1954;6:54–9.
12. Hagbarth KE, Vallbo AB. Pulse and respiratory grouping of sympathetic impulses in human muscle-nerves. *Acta Physiol Scand.* 1968;74:96–108.
13. Esler M, Jackman G, Bobik A, et al. Determination of norepinephrine apparent release rate and clearance in humans. *Life Sci.* 1979;25:1461–70.
14. Blombery PA, Heinzow BG. Cardiac and pulmonary norepinephrine release and removal in the dog. *Circ Res.* 1983;53:688–94.
15. Hasking GJ, Esler MD, Jennings GL, et al. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation.* 1986;73:615–21.
16. Graham LN, Smith PA, Huggett RJ, et al. Sympathetic drive in anterior and inferior uncomplicated acute myocardial infarction. *Circulation.* 2004;109:2285–9.
17. Kishi T, Hirooka Y. Central mechanisms of abnormal sympathoexcitation in chronic heart failure. *Cardiol Res Pract.* 2012;2012:1–7.
18. Triposkiadis F, Karayannis G, Giamouzis G, et al. The sympathetic nervous system in heart failure. Physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol.* 2009;54:1747–82.
19. Esler M. The sympathetic system and hypertension. *Am J Hypertens.* 2000;13 Pt 2:99S–105S.
20. Esler M, Rumantir M, Kaye D, et al. Sympathetic nerve biology in essential hypertension. *Clin Exp Pharmacol Physiol.* 2001;28:986–9.
21. Esler M. The sympathetic system in essential hypertension. *Rev Port Cardiol.* 2000;19 Suppl 2:II9–14.
22. Neumann J, Ligtenberg G, Klein IH, et al. Sympathetic hyperactivity in hypertensive chronic kidney disease patients is reduced during standard treatment. *Hypertension.* 2007;49:506–10.
23. Esler M, Rumantir M, Wiesner G, et al. Sympathetic nervous system and insulin resistance: from obesity to diabetes. *Am J Hypertens.* 2001;14 Pt 2:304S–9S.
24. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. *J Hypertens.* 1997;15 Pt 2:1613–9.
25. Esler M. The 2009 Carl Ludwig Lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transition from mechanisms to medical management. *J Appl Physiol.* 2010;108:227–37.
26. Furlan R, Ardizzone S, Palazzolo L, et al. Sympathetic overactivity in active ulcerative colitis: effects of clonidine. *Am J Physiol Regul Integr Comp Physiol.* 2006;290:R224–32.
27. Fisher JP, Young CN, Fadel PJ. Central sympathetic overactivity: maladies and mechanisms. *Auton Neurosci.* 2009;148:5–15.
28. Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. *Am J Cardiol.* 1978;41:233–43.
29. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:9–13.
30. Esler M, Lambert E, Schlaich M. Point: chronic activation of the sympathetic nervous system is the dominant contributor to systemic hypertension. *J Appl Physiol.* 2010;109:1996–8 [discussion 2016].
31. Schlaich MP, Lambert E, Kaye DM, et al. Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation. *Hypertension.* 2004;43:169–75.
32. Verheye S, Ormiston J, Bergmann M, et al. Twelve-month results of the Rapid Renal Sympathetic Denervation for Resistant Hypertension Using the OneShot™ Ablation System (RAPID) study. *EuroIntervention.* 2014. Epub ahead of print.
33. Sievert H, Schofer J, Ormiston J, et al. Renal denervation with a percutaneous bipolar radiofrequency balloon catheter in patients with resistant hypertension: 6-month results from the REDUCE-HTN clinical study. *EuroIntervention.* 2014. Epub ahead of print.
34. Papademetriou V, Tsioufis CP, Sinhal A, et al. Catheter-based renal denervation for resistant hypertension: 12-month results of the Enlighten I first-in-human study using a multielectrode ablation system. *Hypertension.* 2014;64:565–72.
35. Elmula F, Hoffman P, Larstorp A. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension.* 2014;63:991–9.
36. Rosa J, Widimsky P, Tousek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension.* 2015;65:407–13.
37. Azizi M, Sapoval M, Goose P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet.* 2015;385:1956–65.
38. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet.* 2009;373:1275–81.
39. Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (the SYMPLICITY HTN-2 Trial): a randomised controlled trial. *Lancet.* 2010;376:1903–9.
40. Esler MD, Bohm M, Sievert H, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. *Eur Heart J.* 2014;35:1752–9.
41. Bhatt DL, Kandzari DE, O'Neill WW, et al. SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med.* 2014;370:1393–401.
42. Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J.* 2015;36:219–27.
43. Renal Sympathetic Denervation in Patients with Chronic Kidney Disease and Resistant Hypertension (RSD4CKD). <http://www.clinicaltrials.gov/ct2/show/NCT01737138>
44. Renal Nerve Ablation in Chronic Kidney Disease Patients. <http://www.clinicaltrials.gov/ct2/show/NCT014423883>
45. Renal Denervation in Patients With Uncontrolled Hypertension - SYMPLICITY HTN-4. <http://www.clinicaltrials.gov/ct2/show/NCT01972139>
46. Meissner K, Fassler M, Rucker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. *JAMA Intern Med.* 2013;173:1941–51.
47. Kandzari DE, Kairo K, Mahfoud F, et al. The SPYRAL HTN Global Clinical Trial Program: rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. *Am Heart J.* 2016;171:82–91.