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Endovascular denervation (EDN): From Hypertension to Non-Hypertension Diseases

Tao Pan, Qi Zhang, Jinhe Guo *

Center of Interventional Radiology & Vascular Surgery, Department of Radiology, Zhongda Hospital, Southeast University, 87 Dingjiaqiao Road, Nanjing, 210009, China

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ABSTRACT

Recently, the use of endovascular denervation (EDN) to treat resistant hypertension has gained significant attention. In addition to reducing sympathetic activity, EDN might also have beneficial effects on pulmonary arterial hypertension, insulin resistance, chronic kidney disease, atrial fibrillation, heart failure, obstructive sleep apnea syndrome, loin pain hematuria syndrome, cancer pain and so on. In this article we will summarize the progress of EDN in clinical research.

The sympathetic nervous system (SNS), which mediates the "fight and flight" response to stress,[1] plays a critical role in regulating the cardiac output, blood pressure, and composition of body fluids.[2] Activation of the sympathetic efferent nerves results in reactions that promote survival during states of volume depletion and acute distress.[3] However, sympathetic overdrive contributes to a variety of relevant chronic disease states, including hypertension,[4] insulin resistance,[5] obstructive sleep apnea,[6] heart failure,[7] and renal disease.[8] Therefore, targeting the SNS directly might be an attractive therapeutic approach to simultaneously affect multiple comorbid diseases.

Surgical sympathetic denervation was first used in the early 20th century to treat uncontrolled hypertension in humans.[9] In 1953,[10] a study published the results of paralumbar sympathectomy in 1266 patients with uncontrolled hypertension. Although 65% of patients had long-term improvements in hypertension after surgery, these approaches were associated with significant morbidity and severe complications.[10] Thereafter, the use of surgical sympathectomy to treat hypertension was abandoned. Recent efforts have focused on optimizing minimally invasive procedures and applying new devices to improve these techniques.

With the help of advanced technology and minimally invasive procedures, selective sympathetic denervation has led to the development of a catheter-based device that uses radiofrequency energy for the ablation of sympathetic nerves via arteries. In 2009, Krum et al.[11] first used catheter-based renal denervation (RDN) to treat patients with resistant hypertension, which made endovascular denervation (EDN) a research hotspot. However, the efficacy of RDN on the treatment of resistant hypertension remains controversial. On one hand, lots of percutaneous approaches to increase the specificity with which sympathetic nerves are targeted are currently under development, and new devices that use multi-electrode catheter design have become available[12,13]; on the other hand, in order to treat different diseases, researchers are focusing on targeting different arteries, such as the common hepatic artery,[14] pulmonary artery[15] and celiac artery,[16] to denervate different sympathetic nerves.

EDN is an area of intense research, as the currently available data suffer from potential bias. In this study, we review the technique applied, the clinical evidence for performing EDN in patients with hypertension and non-hypertension diseases, and the potential future indications and limitations of EDN.

Resistant hypertension

Resistant hypertension is defined as uncontrolled hypertension (≥160 mmHg) despite the use of at least three antihypertensive drugs, including a diuretic.[17] Symplicity HTN-1,[11] the first-in-man non-randomized multicenter trial, included 50 patients, of which 45 underwent RDN. Office blood pressure reduced by -27/-17 mmHg at one-year follow-up after RDN, while the mean rise in office blood pressure was +26/+17 mmHg at 9 months in the five non-treated patients. Similar results were shown in a larger series of patients, and post-RDN office blood pressures were reduced by -32/-14 mmHg and -32.0/-14.4 mmHg at 24 and 36 months respectively.[18,19] In addition, in a subgroup of ten patients from Symplicity HTN-1, RDN led to a 47% reduction in norepinephrine spillover at 6 months, indicating that the procedure had indeed targeted the sympathetic nerves.[11]

* Corresponding author. Center of Interventional Radiology & Vascular Surgery, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, 87 Dingjiaqiao Road, Nanjing, 210009, China.
E-mail address: jinheguo@sina.com (J. Guo).

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Following the first proof-of-concept study, Symplicity HTN-2,[20] a randomized controlled clinical trial, was initiated, which randomized 106 patients to either an RDN or control group. At 6 months, office-based blood pressure in the RDN group decreased by 32/12 mmHg, whereas no significant blood pressure reduction was observed in the control group.[20] In addition, a significant blood pressure reduction was persistent at one-year (-28/-9.7 mmHg, n = 49)[21] and three-year (-33/-14 mmHg, n = 40)[22] follow-ups without serious safety concerns.

However, Symplicity HTN-3,[23] a multi-center single blinded trial that randomized 535 patients to either an RDN or sham procedure group, showed no significant reduction in office blood pressure (-14.13 mmHg in the RDN group vs. -11.74 mmHg in the sham-procedure group, $P = 0.26$) or 24-h ambulatory blood pressure reduction (-6.75 mmHg in the RDN group vs. -4.79 mmHg in the sham-procedure group, $P = 0.98$).[23] Despite being a well-designed trial, it was criticized for its race differences and inexperienced operators, and as the quality of RDN was not formally assessed[24,25]; therefore, researchers are still working on the accurate efficacy of RDN. The Renal Denervation for Hypertension (DENERHTN) study[26] enrolled 106 resistant hypertensive patients to either an RDN with standardized stepped-care antihypertensive treatment (SSAHT) group or an SSAHT alone group. At 6 months, the daytime ambulatory systolic blood pressure decreased by 15.8 mmHg in the RDN group and by 9.9 mmHg in the SSAHT group, revealing a baseline-adjusted difference of -5.9 mmHg ($P = 0.0329$). In well-defined resistant hypertensive patients, at 6 months, RDN with an SSAHT decreased ambulatory blood pressure more than the same SSAHT alone.[26]

After Symplicity HTN-3, the field of RDN witnessed improvements in knowledge on factors that implicate denervation efficacy, and histological findings also showed the importance of energy application in the distal vessel segment.[27] Therefore, combined branch and main vessel ablation has become a new technique for RDN. The Symplicity Spyral multielectrode catheter,[28] with four electrodes for positioning, was developed to apply radiofrequency energy circumferentially to all four quadrants of the renal artery and branch vessels. Two international multicenter randomized single-blinded sham-controlled trials, SPYRAL HTN-OFF MED[29] and SPYRAL HTN-ON MED,[30] were designed as new proof-of-concept studies. Patients enrolled in SPYRAL HTN-OFF MED were drug-naive or discontinued their antihypertensive medications, while those in SPYRAL HTN-ON MED were still on one to three antihypertensive drugs with stable doses for at least 6 weeks.[29,30]

In the SPYRAL HTN-OFF MED trial, 80 patients were randomly assigned to the RDN or sham control groups. At 3 months, office and 24-h ambulatory blood pressure decreased significantly in the RDN group: 24-h systolic blood pressure, -5.5 mmHg ($P = 0.0031$); 24-h diastolic blood pressure, -4.8 mmHg ($P < 0.0001$); office systolic blood pressure -10.0 mmHg ($P = 0.0004$); and office diastolic blood pressure, -5.3 mmHg ($P = 0.0002$); no significant changes were observed in the sham-control group.[29] This outcome was recently confirmed in the SPYRAL Pivotal trial,[31] and the treatment differences found between the RDN and sham-control groups were -3.9 mmHg on 24-h systolic blood pressure and -6.5 mmHg on office systolic blood pressure. In addition, significant reduction of blood pressure in the RDN group was reported in the SPYRAL HTN-ON MED study at 6 months, with 24-h systolic blood pressure, -7.0 mmHg ($P = 0.0059$); 24-h diastolic blood pressure, -4.3 mmHg ($P = 0.0174$); office systolic blood pressure, -6.6 mmHg ($P = 0.0250$); and office diastolic blood pressure, -4.2 mmHg ($P = 0.0190$).[30] These results revealed that RDN in the main renal arteries and branches led to more extensive ablation and significantly reduced blood pressure with no major safety events, compared with the sham control.

Furthermore, different devices have been developed to ensure completeness of denervation, and an alternative technology delivering ultrasound energy to thermally ablate the sympathetic nerves has been developed. The RADIANCE-HTN SOLO trial,[32] which uses the Paradise system, randomized 146 patients with mild to moderate combined hypertension into RDN or sham control groups. At 2 months, the reduction in daytime ambulatory systolic blood pressure was 8.5 mmHg in the RDN group, while the decrease was 2.2 mmHg in the sham procedure group ($P = 0.0001$).[32] Moreover, at the 6-month follow-up, despite less intensive SSAHT, RDN had more reduced daytime ambulatory systolic blood pressure than the sham procedure (-18.1 mmHg vs. -15.6 mmHg, $P = 0.024$).[33] In 2019, Fengler et al.[34] performed a study to compare the efficacy of radiofrequency (Symplicity Spyral™ catheter) and ultrasonic (Paradise system) endovascular RDN. They concluded that endovascular ultrasound-based RDN was superior to radiofrequency ablation of the main renal arteries alone, but similar to a combined radiofrequency ablation approach involving the main arteries, accessories, and side branches.[34] Due to these favorable results, most researchers believe that RDN could be effective in strictly selected hypertensive patients, and many trials are ongoing.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a clinical diagnosis consisting of various underlying clinical entities, and can be idiopathic, heritable, drug or toxin-induced, or associated with underlying systemic disease.[35] The pulmonary vasculature receives a rich autonomic nerve supply, with predominantly sympathetic, but also parasympathetic and sensory nerve fibers.[36] Alpha-1 adrenergic receptors in the autonomic ganglia located in the adventitia of the pulmonary vessels seem to play a key role in maintaining an increased vascular tone in pulmonary hypertensive disorders. In animal models of pulmonary hypertension, pulmonary artery denervation (PADN) led to an instantaneous drop in mean pulmonary artery pressure,[37] and PADN has been used clinically since 2013.[15]

Chen et al.[15] performed the first PADN clinical study in low-risk idiopathic pulmonary arterial hypertension patients. The pulmonary artery pressure of 12 patients obviously declined during the subsequent 3 months after PADN, and these patients showed a significant improvement in cardiac input and 6-min walk distance (6MWD) as well. To confirm the efficacy of PADN, Chen et al. then performed other studies that enrolled a variety of patients with disease induced by different causes from different centers.[38–40] They found that performing PADN on the internal surface of the pulmonary artery could still achieve a significant curative effect in patients with pulmonary arterial hypertension, after ablation.

A recent multi-national PADN safety study (TROPHY1) using high-frequency ultrasound around the pulmonary artery bifurcation in PAH patients validated the safety and efficacy of the procedure.[41] In the latest TROPHY1 study, patients with PAH underwent PADN with an intravascular ultrasound catheter without procedure-related adverse events, and revealed significant reduction in pulmonary vascular resistance, and increase in 6MWD and daily activity.[42] In the latest PADN-5 study,[43] patients with both pre- and post-capillary PAH were randomly assigned to PADN or sham denervation plus sildenafil therapy groups. The PADN group showed a significant increase in 6MWD as well as a decrease in pulmonary vascular resistance and pulmonary artery wedge pressure compared to the sham group.

More recently, Romanov et al.[44] reported the results of a randomized, single-blind, sham-controlled study comparing PADN with medical therapy for the treatment of residual PAH after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Fifty patients with residual CTEPH were randomized to the PADN group or the medical therapy with riociguat (MED) group. At 12 months, the mean reduction in pulmonary vascular resistance between the groups was 109 dyn·s·cm^{-5} ($P = 0.001$), and 6MWD was significantly increased in the PADN group compared to that in the MED group (470 ± 84 m vs. 399 ± 116 m, respectively; $P = 0.03$); however, clinical worsening occurred more frequently in the MED group.[44] The available data suggest that the ablation procedure is safe and feasible, but careful studies involving homogeneous patient populations are needed to further determine its procedural safety and long-term effects on hemodynamics, functional capacity, and outcomes.[45]

Insulin resistance

SNS activation is associated with insulin resistance, which is considered essential for the pathogenesis of type 2 diabetes mellitus (T2DM), and the resultant hyperinsulinemia causes further sympathetic excitation, establishing a self-perpetuating cycle.[46,47] In 2011, preliminary evidence showed that RDN might re-establish metabolic balance and attenuate insulin resistance.[48–50] In a population of 50 patients with resistant hypertension and containing 40% T2DM patients divided into an RDN group and a conventional treatment group, a significant improvement in glucose metabolism was found in the RDN group. Specifically, fasting glucose reduced from 118 mg/dL to 108 mg/dL ($P = 0.039$), insulin levels reduced from 20.8 mIU/mL to 9.3 mIU/mL ($P = 0.006$), C-peptide levels decreased from 5.3 ng/mL to 3.0 ng/mL ($P = 0.002$), and homeostasis model assessment-insulin resistance (HOMA-IR) improved from 6.0 to 2.4 ($P = 0.001$).[48]

In another small prospective study of 10 sleep apnea patients demonstrating similar results, Witkowski et al. found a significant reduction in blood pressure and apnea–hypopnea index, as well as significant reduction of plasma glucose concentration 2-h after oral glucose tolerance test from 7.0 mmol/L to 6.4 mmol/L ($P = 0.05$) and decrease of hemoglobin A1c from 6.1% to 5.6% ($P < 0.05$) 6 months after RDN.[49] A similar improvement was noted in two polycystic ovarian syndrome cases: after both patients underwent RDN, fasting plasma glucose declined, and insulin sensitivity improved by 17.5% in the presence of unaltered body weight at the 3-month follow-up.[50] The possibility observed in these studies may open a promising nonpharmacological strategy for patients with T2DM.

However, the DREAMS-Study[51] investigated the effects of RDN on insulin sensitivity and blood pressure in 29 patients with metabolic syndrome, of whom 5 (17%) had T2DM, and it contradicted the results mentioned above. Fasting glucose changed from 7.2 mmol/L to 7.4 mmol/L at 6-month follow-up ($P = 0.34$) and 7.0 mmol/L at 12-month follow-up ($P = 0.34$). Median insulin sensitivity did not change at the half- and 1-year follow-up ($P = 0.60$, and $P = 0.77$, respectively). In addition, muscle sympathetic nerve activity did not change after RDN: 48 bursts/min and 75 bursts/100 heartbeats at the 6-month follow-up vs. 48 bursts/min ($P = 0.86$) and 74 bursts/100 heartbeats ($P = 0.80$) at baseline. These results showed that RDN did not change fasting glucose, median insulin sensitivity, or systemic sympathetic activity.[51]

The currently used catheter did not adequately lower sympathetic nervous system activity, possibly due to insufficient denervation, and this might have resulted in the finding of the DREAMS-Study [46]; therefore, researchers have wondered whether a multielectrode catheter could achieve better outcomes. In a study by Tsioufis,[52] the EnligHTN multielectrode RDN system was used to perform the procedure in 17 enrolled patients with metabolic syndrome. At 3 months, although no significant change was observed in HOMA-IR, patients in the RDN group had a restored normal neural response to oral glucose loading and reduced elevated sympathetic nerve activity.[52] In another study of 31 resistant hypertensive patients, including 22 normoglycemic and 9 patients with impaired fasting glucose who underwent RDN, fasting glucose (97.1 mg/dL vs. 92.3 mg/dL; $P = 0.010$), hemoglobin A1c levels (5.82% vs. 5.58%; $P = 0.008$), and HOMA-IR (2.25 vs. 1.94; $P = 0.004$) were significantly reduced at 6 months.[53] In addition, there was a significant increase in pro-insulin, C-peptide, and insulin concentrations 6 months after RDN (all $P < 0.001$) due to stimulation with glucagon, which revealed improvement in the secretory capacity of beta-cells and possible attenuation of the development of T2DM.[53]

At the same time, different targeted arteries have been under investigation. Recently, in an animal study of fat- and fructose-fed dogs, surgical sympathetic denervation of the common hepatic artery was performed.[14] The procedure reduced the diet-induced defect in net hepatic glucose balance by 37%, which continued for 3 months on follow-up and showed the potential to enhance postprandial glucose clearance. In another animal study, male C57BL/6J mice fed a high-fat diet were used as chronic hepatic sympathetic overactivity-mediating hepatic steatosis models.[54] Two approaches, including the pharmacological ablation of the sympathetic nerves and phenol-based hepatic sympathetic nerve denervation, were used to reduce hepatic sympathetic nerve activity. After the procedure, high-fat diet-induced hepatic steatosis was effectively reduced without changes in body weight, caloric intake, or adiposity, which was associated with improvements in liver triglyceride accumulation pathways.

The celiac plexus mainly includes four branches: the anterior hepatic plexus, posterior hepatic plexus, splenic plexus, and plexus accompanying the transverse pancreatic artery, which are distributed in different locations in the human pancreas. Sympathetic afferents are thought to exit the pancreas along the postganglionic sympathetic fibers, within the splanchnic nerves and the celiac plexus, to the dorsal root ganglia.[55,56] It is reasonable that the celiac artery may be the potential target artery for performing EDN, and further evaluation in the arteries and rigorously designed clinical trials will be necessary to confirm the benefits of EDN in patients with T2DM.

Chronic kidney disease

SNS activation plays a critical role in chronic kidney disease (CKD), which is evident in the early phases of the disease and closely related to target organ damage and cardiovascular and total mortality in patients with end-stage renal disease.[57,58] In 100 resistant hypertensive patients who underwent RDN, renal resistance indices were improved at 3-month and 6-month follow-ups, accompanied by a decrease in the severity of macroalbuminuria and microalbuminuria.[59] In another study of 46 CKD patients who underwent RDN, linear mixed model analysis demonstrated a significant progressive decline in estimated glomerular filtration rate (eGFR) from 60 months to 12 months, and from 12 months to the baseline prior to RDN. RDN was associated with improved eGFR at 3 months, and no significant changes at 6, 12, and 24 month follow-up were observed.[60] Recently, long-term data from the Global SYMPLICITY Registry representing the results of 1742 patients 3-year after RDN revealed that renal function declined by 7.1 mL/min/1.73 m^2 in patients without CKD and by 3.7 mL/min/1.73 m^2 in patients with CKD, without any long-term safety concerns.[61] In view of the currently available device-based treatments, RDN remains a valuable tool to slow the rate of progression of CKD and its complications, but whether this might translate to improved patient outcomes warrants further research.

Atrial fibrillation

The autonomic nervous system plays an important role in atrial fibrillation (AF), and the association of the key pathophysiology of sympathetic overdrive with hypertension and AF provides a rational basis for therapeutic strategies, such as combined RDN and pulmonary vein isolation (PVI), in patients with hypertension and AF.[62] In 2012, Pokushalov et al.[63] first reported 27 patients with moderate hypertension and AF who were treated with PVI alone and in combination with RDN. A lower rate of recurrence of AF in the PVI + RDN group, compared with PVI alone group (69 vs. 29%, $P = 0.033$), was found at 12-month follow-up. This result was confirmed in a subsequent study that enrolled patients with severe hypertension, in which the ratio of AF-free patients was 61% in the PVI + RDN group and 28% in the PVI alone group ($P = 0.03$).[64] Recently, the ERADICATE-AF trial,[65] a multicenter single-blind randomized clinical trial, was conducted to determine whether RDN with PVI could enhance long-term antiarrhythmic efficacy. A total of 302 patients were randomized to either PVI alone (n = 148) or PVI + RDN (n = 154) groups, and 283 (93.7%) completed the trial. At 12 months, PVI + RDN, compared with PVI alone, resulted in a statistically significantly greater proportion of patients who were free from atrial fibrillation over 12 months (72.1% vs. 56.5%, $P = 0.006$).[65] However, the lack of a formal sham procedure should be considered when interpreting the results.

Heart failure

Despite the complexities of heart failure, a global pandemic with a poor prognosis even after hospitalization, it is universally accepted that significant sympathetic overactivity occurs in patients with advanced clinical heart failure.[66] The REACH-Pilot study,[67] the first-in-man safety evaluation of RDN for chronic systolic heart failure, enrolled seven patients, and over six months, despite a non-significant trend in blood pressure reduction, all the patients described themselves as symptomatically improved, and the 6MWD was significantly increased. However, the Symplicity HF Feasibility Study enrolled 39 patients with chronic systolic heart failure and renal impairment on stable medical therapy, and statistically significant reductions in N-terminal pro-B-type natriuretic peptide and 120-min glucose tolerance test were observed at 12 months, but there was no significant change in left ventricular ejection fraction, 6MWD, or eGFR.[68] In a recent randomized controlled trial, 60 patients with chronic systolic heart failure were randomly assigned to the RDN or control groups, and at the 6-month follow-up, when compared with the control group, patients in the RDN group showed a decrease in N-terminal pro-B-type natriuretic peptide (440.1 pg/mL vs. 790.8 pg/mL, $P < 0.001$), an increase in left ventricular ejection fraction (39.1% vs. 35.6%, $P = 0.017$), improved New York Heart Association class assessment ($P = 0.01$), and decreased blood pressure ($P < 0.001$).[69] Nevertheless, the long-term effects of RDN on heart failure remain unclear.

Obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) is an independent cardiovascular risk factor characterized by recurrent upper airway obstruction and increased sympathetic activity that likely plays an essential role in the development of resistant hypertension.[70] In a prospective study of 10 patients with OSAS, Witkowski et al.[49] reported that apnea-hypopnea index decreased from 16.3 events per hour to 4.5 events per hour ($P = 0.059$) 6 months after RDN. In another small study, two responders with OSAS showed improved polysomnography indices, and one with left concentric ventricular hypertrophy showed complete cardiac remodeling 11 months after RDN.[71] In a randomized proof-of-concept phase II trial,[72] 60 patients with true resistant hypertension coexisting with moderate-to-severe OSAS were randomly allocated to a RDN group and a control group. At 3 months in the RDN group, a significant decrease in OSA severity (apnea/hypopnea index, 39.4 events per hour vs. 31.2 events per hour; $P = 0.015$) was observed, and a significant improvement in echocardiographic measures of global longitudinal strain was found at 6 months in the RDN group.[72] Further studies are warranted to assess the impact of RDN on OSAS and its relationship with blood pressure decline and cardiovascular risk.

Loin pain hematuria syndrome

Loin pain hematuria syndrome (LPHS) is a painful and incapacitating condition that typically affects young women, with microscopic or macroscopic hematuria, although the renal abnormalities responsible for hematuria are often unexplained.[73] Prasad et al.[74] first used the Vessix RDN system to perform endovascular ablation of the renal nerves in four patients with LPHS. By 6 months, improvements in pain, disability, and quality of life were found, and two of four patients had discontinued all pain medications, whereas the other two had reduced their doses of these medications by 75%. In their following research,[75] 12 patients with LPHS who underwent endovascular ablation were enrolled. Ten of 12 patients at 3 months, and 11 of 12 patients at 6 months reported over 30% reduction in pain, as well as considerable improvement in pain, disability, quality of life, and mood. The initial improvement in pain observed in these patients opens up the possibility of conducting further clinical studies of LPHS with RDN, and long-term clinical studies are needed to fully evaluate the beneficial effects of RDN.

Cancer pain

Pain is a common and debilitating problem for patients with malignancies, and about 67% of patients with cancer experience pain or take narcotics for prolonged periods of time.[76] An alternative to opioid therapy is celiac plexus neurolysis, and endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) has been introduced.[77] In 2018, Qi Zhang et al.[16] performed a study on seven cancer pain patients to appraise the feasibility and safety of using EDN for cancer pain, with EDN carried out at the abdominal aorta close to the origin of the celiac artery and superior mesenteric artery using a multielectrode radiofrequency ablation catheter. The pain scores at 1, 2, 4, 8, and 12 weeks after EDN were significantly lower than those before the operation ($P < 0.001$), and a significant reduction in narcotic use and better sleep within 3 months after EDN were also observed. It was commented, "Although only 7 patients were treated in this pilot study, the results are extremely promising, with significant reductions in pain and opioid agent use and increased quality of life (QOL) in physical, psychologic, and level-of-independence domains with no severe adverse toxicity."[78] Future avenues of research could include a randomized clinical trial comparing the outcomes of EDN with celiac plexus neurolysis for patients with advanced abdominal cancer.

Conclusions

Sympathetic denervation, which moderates SNS to improve physiological parameters, has the potential to treat some of the most challenging and common cardiovascular conditions. Despite the failure of SYMPLICITY HTN-3, recent evidence in many alternative areas has the potential to overcome current therapeutic hurdles. New devices, including RF ablation catheters, intravascular ultrasound catheters, perivascular pharmacological ablation, and externally applied focused ultrasound, are currently being investigated for the delivery of more ablation, including those to areas distal to arterial bifurcations. Continued exploration of the pathophysiological basis of sympathetic denervation could eventually accurately target the most appropriate artery and identify the most suitable procedure for the treatment of a large population of patients with various diseases. Well-designed trials should include a sham control arm and delineate confounding factors that can affect our understanding of EDN efficacy. Over a 100 registered RCT trials are currently designed to address these questions and formulate new avenues of inquiry.

Declaration of competing interest

All the authors disclose none actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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