Renal Sympathetic Denervation – A Review of Applications in Current Practice

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Abstract

Resistant hypertension is associated with high morbidity and mortality despite numerous pharmacological strategies. A wealth of preclinical and clinical data have demonstrated that resistant hypertension is associated with elevated renal and central sympathetic tone. The development of interventional therapies to modulate the sympathetic nervous system potentially represents a paradigm shift in the strategy for blood pressure control in this subset of patients. Initial first-in-man and pivotal, randomised controlled trials of endovascular, radio-frequency renal sympathetic denervation have spawned numerous iterations of similar technology, as well as many novel concepts for achieving effective renal sympathectomy. This review details the current knowledge of these devices and the evidence base behind each technology.

Keywords

Hypertension, devices, resistant, renal sympathectomy

Disclosure: Vikas Kapil has received funding from the British Heart Foundation. Ajay K Jain is an Advisory board member for Medtronic Inc. Lobo received educational grant funding from Medtronic Inc., is a Consultant to and is on the speakers' bureau of St Jude Medical and is a Consultant to ROX Medical and CardioSonic.

Received: 2 December 2013 **Accepted:** 18 February 2014 **Citation:** *Interventional Cardiology Review*, 2014;9(1):54–61

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Up to one-in-five treated hypertensive patients are deemed to be treatment resistant^{1–3} (on at least three different anti-hypertensive medication classes, including a diuretic)^{4–6} and have high cardiovascular risk.^{7–9} There is a paucity of high-quality evidence to suggest that the addition of a fourth line (or fifth, sixth line, etc.) medication is likely to bring either hypertension under control or to reduce excess morbidity/mortality in resistant hypertension (RHTN).⁵ Recently, renal sympathetic denervation (RSD) has been suggested as an effective, evidence-based approach for controlling RHTN.¹⁰

The Rationale for Renal Sympathetic Denervation in Human Resistant Hypertension

Activation of the sympathetic nervous system (SNS) is now recognised to occur in all stages of hypertension and correlates to the severity of hypertension.^{11,12} The renal efferent and afferent SNS neural fibres make their own contribution to the maintenance of the hypertensive phenotype. Renal SNS afferents run along the renal artery adventitia and cluster in the renal pelvis^{13,14} and activity of these renal SNS fibres regulate whole body sympathetic tone by moderating hypothalamic activity.¹⁵ Renal SNS efferents innervate the kidneys from the para-vertebral ganglia at T10-L2 and also run alongside the renal afferents in the renal artery adventitia.¹³ Renal SNS efferent activity mediates renal sodium retention, volume expansion¹⁶ and stimulates the neuro-humoral renin–angiotensin–aldosterone axis, further elevating blood pressure (BP) through salt/water retention and vasoconstriction.¹⁷

In the first half of the 20th century, surgical thoracolumbar sympathectomy (resulting in renal sympathectomy) was performed to treat malignant hypertension with good results in terms of reducing both BP and mortality.^{18,19} However, this radical surgical operation was not without significant operative mortality and post-operative morbidity, including postural hypotension, erectile dysfunction and syncope.

Thus the procedure fell out of favour with the advent of anti-hypertensive medications that were non-invasive, tolerable and proved to reduce BP and mortality.²⁰

Preclinical studies have clearly demonstrated that interruption of renal SNS signalling, by either surgical ligation and re-anastomosis or chemical adventitial stripping of the renal artery, prevents the development of hypertension and, furthermore, attenuates established hypertension in numerous animal models of hypertension.²¹ Further evidence for benefit of renal sympathectomy in the treatment of hypertension comes from a study of patients treated with bilateral nephrectomy for end-stage chronic kidney disease (CKD) maintained on haemodialysis or post-transplantation, which demonstrates sustained BP reduction.²² While these techniques are not suitable for use in humans, the recent development of minimally invasive, catheter-based solutions^{10,23} to effect selective RSD has re-ignited interest in this field.

Figure 1: Current Renal Sympathetic Denervation Technologies

Medtronic Inc. first-generation Symplicity™ (a) and second-generation Symplicity Spyral™ (b) radio-frequency (RF) catheters; St Jude Medical multi-electrode, basket design EnLIGHTN RF catheter (c); ReCor Medical Paradise™ circumferential irrigated balloon, ultrasound (US) catheter (d); Covidien One-Shot™ spiral RF catheter (e); Biosense ThermoCOOL™ irrigated multi-electrode RF catheter (f); CardioSonic TIVUS™ balloon US catheter (g); Verve Medical™ retro-ureteric multi-electrode basket RF catheter (h); Boston Scientific Vessix™ multi-electrode, balloon-mounted, bipolar RF catheter (i) and Mercator Bullfrog™ micro-needle catheter for perivascular guanethidine injection (j).

Current Technologies for Renal Sympathetic Denervation

The paradigm for a technology that may have utility in renal SNS modulation for hypertension is that it achieves selective RSD with no collateral damage to adjacent/other structures. The different technologies that are currently being tested in both preclinical and clinical studies vary in their potential benefits and pitfalls and these issues are discussed below.

Radio-frequency Neural Ablation

Radio-frequency (RF) energy, introduced for ablation of neurovascular tissue more than 25 years ago,²⁴ is an alternating electrical current that produces tissue destruction by both direct resistive heating of the tissue in contact with the catheter tip and by thermal conduction to deeper tissue. The RF electrical current is delivered most frequently in the unipolar mode, with completion of the electrical circuit via another electrode placed on the skin. In bipolar mode, two closely opposed electrodes are placed on the catheter electrode tip. On energy delivery to the target surface, the catheter tip heats subjacent (up to 4 mm) tissues from 50 to 70°C.²⁵ A sudden rise in impedance can suggest over-heating and charring of tissue at the tip and many modern RF catheters are designed with auto-feedback mechanisms to prevent excessive temperature elevations. Other factors that influence tissue destruction include duration of energy application, with at least 35 seconds required for uniform temperature elevations in targeted tissue,²⁶ catheter electrode size and tissue apposition and the level of power applied from the RF generator.

Anatomical considerations are required before progressing to RF RSD.²⁷⁻²⁹ Prior renal artery duplex scanning or cross-sectional imaging to rule out significant renal atherosclerotic disease is required, and this is confirmed at the time of endovascular RSD by formal angiography before ablation catheter placement. The main trunk diameter should be >4 mm and the length should be >20 mm to allow both effective blood flow for cooling (see below) and sufficient space for multiple ablations. Furthermore, accessory or dual arteries should be of similar dimensions to allow treatment to be given to all arteries concurrently. To date, RF RSD is not recommended in patients with previous renal artery angioplasty or endovascular stents to treat previous atherosclerotic renal artery stenosis (RAS).

First-generation RF RSD systems utilise flexible RF catheters that are advanced into each renal artery in turn under fluoroscopic guidance. Energy delivery causes thermal destruction of SNS neural tissue in the perivascular adventitia and using native renal blood flow to cool the intima, endothelial damage is reduced. Intra-procedural utilisation of vasodilators, such as nitroglycerine (glyceryl trinitrate) and non-dihydropyridine calcium channel blockers, are often used to prevent vasospasm that may accompany energy delivery. The perivascular neural bundle also contains sensory C fibres and thus neural destruction is accompanied by significant pain, necessitating conscious sedation and adequate opiate-based analgesia.

Ardian Inc. (later purchased by Medtronic Inc.) developed the first minimally invasive technology to effect selective RSD. The

Table 1: Radiofrequency Technologies for Renal Sympathetic Denervation

Device (Company, CE Mark)	Catheter/Anatomy Details	Technical Details	Development Phase
Symplcity™ Medtronic Inc. Minneapolis, US CE: February 2008	6 Fr, no guidewire Unipolar, mono-electrode Renal artery: >4 mm	8 watts 2 minute/ablation >4 ablation/artery Cooling: blood flow	Clinical: see text for first-in-man and randomised control trial results ^{10,31} Double-blind, sham-controlled (Symplcity HTN-3, n=530) failed primary efficacy 6 month OBP end-point (NCT01418261)
Symplcity Spyr™ Medtronic Inc. Minneapolis, US CE: Not available	6 Fr, over-the-wire Unipolar, 4-electrode Catheter helically conforms to artery Renal artery: 3–8 mm	8 watts 1 minute/ablation 1 ablation/artery Cooling: blood flow	Clinical: [abstract] observational (n=50) to 6 month post RSD Severe RHTN, on >2 meds Interim results (n=29, 1m); baseline OBP: 182/94 mmHg ↓OBP: 16/7 mmHg ³⁸
EnligHTN™ St Jude Medical St Paul, US CE: December 2011	8 Fr, no guidewire Unipolar, 4-electrode Basket mounted (6 or 8 mm) Renal artery: 4–8 mm	6 watts 90 second/sequential ablation per electrode 2 ablation/artery Cooling: blood flow	Clinical: EnligHTN-1; observational (n=46) to 6 month Severe RHTN, on >2 meds, baseline OBP: 176/96mmHg ↓OBP: 26/10 mmHg 6m Check CTA: no new RAS ³⁰
One-Shot™ Covidien Ltd CE: February 2012 Dublin, Ireland Withdrawn January 2014	7–8 Fr, over-the-wire Unipolar, balloon-mounted, Low-pressure balloon (<1 atmosphere) helical electrode Renal artery: 4–7 mm	25 watts 2 minute/ablation Cooling: irrigated (8-hole) 1 ablation/artery catheter tip	Clinical: RHAS; observational (n=9) to 12 months post RSD Treated hypertension, on >1 med, baseline OBP 186/91 mmHg ↓OBP: 31/10 mmHg (12m), ↓ABP: 3/4 mmHg (6 months) 6 month check CTA: no RAS at 12 months ³⁹
ThermoCOOL™ Biosense Webster Diamond Bar, US CE: May 2012	7 Fr, over-the-wire Unipolar, 4-electrode Renal artery: >4 mm	10–20 watts 30 second/ablation 4–6 ablation/artery Cooling: irrigated (6-hole) catheter tip	Clinical: Observational (n=10) to 6 month post RSD Moderate RHTN, on >2 meds, baseline ABP: 158/88mmHg ↓ABP: 21/10 mmHg Repeat renal angiography at 3 months: no RAS ⁴⁰
Vessix™ Boston Scientific Natick, US CE: May 2012	8 Fr, over-the-wire Bipolar, balloon-mounted, 8-electrode pairs Non-compliant balloon (3 atmosphere, 4–7 mm) Renal artery: 3–7 mm	1 watt 30 second/ablation 1–2 ablation/artery Cooling: blood flow	Preclinical: [abstract] porcine (n=17) to 6 months post RSD; Chronic, destructive neural changes at 6 months Increased small nerve growth at 6 months, uncertain significance ³¹ Clinical: reduce HTN; (n=150, NCT01541865) unpublished data
Iberis™ Terumo Corp. Tokyo, Japan CE: April 2013	4 Fr, no guidewire Unipolar, mono-electrode Radial access Renal artery: >4 mm	8 watts 2 minute/ablation >4 ablation/artery Cooling: blood flow	Clinical: case report (n=1) to 2 week post RSD Severe RHTN on 4 meds, baseline OBP 160/90mmHg ↓OBP: 15/10mmHg ⁴²
Verve™ Verve Medical Santa Barbara, US CE: Not available	9 Fr, over-the-wire Unipolar, multi-electrode Retro-ureteric No systemic contrast	Low power 1 ablation/renal pelvis Cooling: urinary flow	Preclinical: porcine (n=16) study to 30 day post-RSD Imaging: normal pyelography, angiography 7–30 day Histology: renal artery safety; SNS neural ablation ↓renal NE by ~60 % ⁴³

ABP=ambulatory blood pressure; CTA=computed tomography angiogram; eGFR=estimated glomerular filtration rate; meds=medications; NE=norepinephrine; OBP=office blood pressure; RAS=renal artery stenosis; RHAS=renal hypertension ablation system; RHTN=resistant hypertension; RSD=renal sympathetic denervation; SNS=sympathetic nervous system.

Symplcity™ (Minneapolis, US) catheter consists of a unipolar ablation catheter and a proprietary low-energy RF generator, and is the most widely used and studied device to date. Typically four to seven ablations (5 mm apart; 2 minutes per ablation) are performed sequentially in each artery in a classic helical pattern distally to proximally to prevent potential RAS and cover the full arterial circumference.

Symplcity HTN-1 was a non-randomised, first proof-of-concept study using the Symplcity system in severe RHTN (n=45; office BP=177/101 mmHg; mean anti-hypertensive medications=4.7) demonstrating improvement of office BP by 27/17 mmHg at 12-months¹⁰ and by 32/14 mmHg at 36 months.³⁰ Symplcity HTN-2 was a randomised trial of RSD (using the Symplcity catheter) plus current treatment versus current treatment only. In patients randomised to RSD (n=49; office BP=178/97 mmHg; mean anti-hypertensive medications=5.2), 6-month office BP-lowering was 32/12 mmHg compared with 1/0 mmHg in controls (n=51).³¹

Since the publication of these initial studies using the Symplcity catheter, other devices have quickly come to the market and tried to establish their own safety and efficacy profiles (see *Figure 1*; *Tables 1–3*), with improved technological iterations on the original Ardian Inc. design. Recently, the first dedicated radial-approach RSD device has gained a CE mark (Iberis™, Terumo Corp, Tokyo, Japan) (see *Table 1*). This is a unipolar electrode similar to the Symplcity system that is introduced via the trans-radial approach rather than the trans-femoral approach. This trans-radial approach has been shown to be associated with reduced access-site complications in percutaneous coronary interventions (PCI) and is recommended as the default site for access in PCI.³²

Several companies have designed multi-electrode or elongated, spiral electrode catheters, including a second-generation catheter from Medtronic Inc., which can produce simultaneous energy applications at multiple anatomical sites within the renal artery,

Table 2: Ultrasound Technologies for Renal Sympathetic Denervation

Device (Company, CE Mark)	Catheter/Anatomy Details	Technical Details	Development Phase
Paradise™ ReCor Medical Menlo Park, US CE: December 2011	6 Fr, over-the-wire Cylindrical transducer Transducer in low-pressure, 5–8 mm cylindrical, centring balloon Renal artery: 4–8 mm	25–30 watts, non-focused US Circumferential 40 second/ablation; <3 ablation/artery Cooling: closed circuit irrigated balloon	Preclinical: [abstract] porcine (n=11) renal artery safety at 7–28 days post RSD ⁹³ Clinical: REDUCE; observational (n=11) to 3 months post RSD Moderate RHTN on >2 meds, baseline OBP: 180/109 mmHg ↓OBP: 36/17 mmHg; ↓HBP: 22/12 mmHg Stable renal function at 3 months post RSD (data not provided) ⁹⁴
TIVUS™ CardioSonic Tel Aviv, Israel CE: Not available	6 Fr, over-the-wire Cylindrical transducer Renal artery: >4 mm	8 watts, high-intensity, non-focused US Circumferential 30 second/ablation; <3 ablation/artery Cooling: blood flow	Preclinical: unpublished porcine renal safety data Clinical: unpublished observational (n=17) first-in- man study
Sound 360™ Sound Interventions Stony Brook, US CE: Not available	8 Fr, no guidewire Cylindrical transducer Transducer in low-pressure, triangular, centring balloon Renal artery: >5 mm	Low-power, high-intensity, non-focused US Circumferential 2 minute/ablation; 2 ablation/artery Cooling: blood flow	Clinical: [abstract] sound-interventions; observational (n=10) to 1 month post-RSD Severe RHTN on >2 meds, baseline office systolic blood pressure >160 mmHg ↓OBP: 31/10 mmHg Post-RSD angiography and IVUS, no change arterial size ⁹⁵
Surround Sound™ Kona Medical Campbell, US CE: Not available	External applied US energy Renal artery: Not available	Low-intensity, focused US 3 minute/ablation; 1 ablation/artery Cooling: Not available	Clinical: [abstract] WAVE II; observational (n=13) to 6 week post-RSD Moderate RHTN on >2 meds ↓OBP: 18/0 mmHg No significant adverse events ⁹⁶

HBP=home blood pressure; IVUS=intravascular ultrasound; OBP=office blood pressure; RSD=renal sympathetic denervation; RHTN=resistant hypertension; US=ultrasound.

either mounted externally on a scaffold or inflatable balloon (see Table 1). Not only does this substantially reduce procedure time and contrast load but it may also help achieve complete circumferential nerve ablation, as the catheter does not need to be re-positioned between energy applications. Even more recently, 3D electrical current mapping technology, commonly applied in cardiac electrophysiology (EP) procedures, has been used to further reduce both contrast load and radiation exposure.³³

Further iterations of RF RSD devices include integrated cooling mechanisms to prevent local tissue heating to excessive levels (see Table 1). First-generation systems have utilised concurrent renal artery blood flow to aid cooling of the endothelium to prevent thermal damage. Computational modelling has recently indicated that the intrinsic rate of renal artery blood flow, which cannot be easily manipulated peri-procedurally, is crucial in controlling both the direct, local (i.e. thermal effects to arterial wall) and distant (i.e. thermal effect on blood) effects of RF RSD.³⁴ To counteract these effects, saline-irrigated RF catheters have become a standard design for cardiac EP ablations and have been shown to reduce contact-tissue heating without reducing the destruction of deep target tissue.³⁵ Preliminary preclinical data in swine suggest that irrigated RF RSD ablation using the ThermoCOOL™ system (Biosense Webster Inc. [Diamond Bar, US] [see Table 1]) reduced arterial media and peri-arterial collagen damage but produced similar neural destruction compared with non-irrigated RF RSD procedures in arteries harvested 10 days post-procedure.³⁶

Endothelial damage is a serious concern with non-irrigated RF RSD devices as it has been demonstrated with the use of optical coherence tomography (OCT) imaging that first-generation RF RSD

catheters (Symplicity and EnligHTN™ [St Jude Medical, St Paul, US] systems) caused diffuse renal artery vasospasm, local tissue oedema and thrombus,^{37,38} suggesting the potential need for concurrent, peri-procedural anti-platelet therapy.³⁷ This may well be a temporary phenomenon and the clinical significance of these imaging findings is not currently known. Reassuringly, preclinical porcine studies using the Symplicity catheter showed no significant RAS, smooth muscle hyperplasia or thrombosis angiographically or histologically at 6 months post RF RSD.²³ Follow-up renal imaging in the Symplicity trials has indicated only one novel RAS as a sequela of RF RSD in 88 patients followed for up to 3 years.³⁰ Furthermore, renal safety has recently been explored in 15 patients with RHTN and moderate to severe CKD stages 3–4) that would have been excluded from the Symplicity HTN-1 and HTN-2 trials. This study revealed preservation of renal function to 12 months after RSD,³⁹ which provides limited but further encouraging data regarding renal safety.

The potential damage caused by RF energy application direct to the renal artery endothelium means that it may not be the optimal technology for endovascular RSD. Other non-RF technologies, described below, are being developed to overcome some of these concerns. Interestingly, the proximity of the renal nerves to the renal pelvis has led to the development of a non-endovascular approach to RF-mediated RSD. Verve Medical (Santa Barbara, US) have developed an eponymous, retro-ureteric delivered RF device that has been tested in preclinical porcine studies, with reduction in renal tissue norepinephrine (NE) levels and no significant vascular or renal parenchymal damage up to 30 days post-procedure.⁴⁰ This approach prevents patient exclusion for renal arterial anatomical reasons that was common in the Symplicity RSD clinical studies,^{10,31} but other urological pathologies may prevent usage of this approach in certain patients.

Table 3. Chemical Technologies for Renal Sympathetic Denervation

Device (Company,CE Mark)	Catheter/Anatomy Details	Technical Details	Development Phase
Bullfrog™ Mercator MedSystems Inc. San Leandro, US CE: Not available	6 Fr, over-the-wire Renal artery: 2–6 mm	Balloon-sheathed micro-needle (30 G) Balloon Inflation (2 atmosphere) exposes micro-needle Peri-adventitial delivery of guanethidine 50 mg in 6 mL	Preclinical: porcine (n=15) to 28 days post RSD Renal nerve rarefaction, reduced renal NE level No renal artery morphological changes Undetectable plasma (guanethidine) 1 day post RSD 54 ng guanethidine/g renal tissue 28 days post RSD ⁹⁷
Peregrine™ Ablative Solutions Kalamazoo, US CE: Not available	7 Fr, over-the-wire 3 guide-tubes to centre catheter Renal artery: not known	Tube-sheathed micro-needles (3x32 G) Peri-adventitial delivery of 0.15-0.6 mL dehydrated ethanol	Preclinical: porcine (n=12) to 14–45 days post RSD Dose-dependent reduction in renal NE levels (14 days) Histological confirmation of neural injury Angiography normal (45 days) post RSD ⁹⁸
ApexNano™ ApexNano Therapeutics Herzliya, Israel CE: Not available	Standard catheter Renal artery: not known	40–80 nM magnetic nanoparticles Internal/external magnetic field steer particles to renal artery wall Modulation of magnetic field releases Botox®	No published data
No name University of Athens Athens, Greece CE: Not available	7 Fr, over-the-wire Triple lumen, double-balloon catheter 6 side-holes (25 µM) Renal artery: not known	0.1 mg vincristine delivered directly against renal artery wall Balloon occludes lumen to prevent systemic escape of vincristine	Preclinical: Porcine (n=14–16) to 28 days post RSD Renal nerve rarefaction and arterial safety ^{44,55} Clinical: Case-report (n=1) to 4 weeks post RSD Severe RHTN on 4 meds, baseline OBP 174/102 mmHg ↓OBP: 40/22mmHg; ↓ABP: 23/13mmHg Stable renal function at 4w (data not provided) ⁵⁶

ABP=ambulatory blood pressure; NE=norepinephrine; OBP=office blood pressure; RSD=renal sympathetic denervation; RHTN=resistant hypertension.

Ultrasound Neural Ablation

Ultrasound (US) energy delivers sound waves >20 Hz. When US is directed against a medium that is able to absorb the energy, it is converted to thermal energy within that medium. It can be delivered without vessel contact, with US waves passing through fluid/interposing tissue to heat target tissue to generate targeted thermal injury. It has been established as an effective therapy for cardiac EP procedures.⁴¹ Different approaches have been developed to harness the potential utility of US for RSD with the proposed benefits over RF ablation being controlled and greater depth of denervation and endothelial sparing (see Table 2). The requisite depth for effective denervation is, however, debatable as the majority of human SNS fibres have been shown to lie within 2 mm of the renal arterial lumen¹⁴ and deeper denervation techniques may pose harm to adjacent structures including the psoas muscle (posteriorly) and bowel within the peritoneal space (anteriorly).

While extra-corporeal high-intensity focused US (HIFU) has long been used to ablate deep, solid tissue tumours through thermal injury⁴² and has recently been tested in preclinical canine studies of RSD,⁴³ the use of extra-corporeal, low-intensity focused US (LIFU) for RSD represents an entirely unique and potentially non-invasive strategy that is particularly attractive (see Table 2). The mechanism of tissue damage by LIFU is not entirely characterised and is thought to be predominantly sono-mechanical (i.e. vibration-induced cellular damage) rather than thermal.⁴⁴ Although the Surround Sound™ system from Kona Medical (Campbell, US) is currently using a targeting catheter in its early phase development, the stated aim of the company is to develop a fully non-invasive technology that applies LIFU without the requirement for endovascular access. One could imagine such a technology being easily translatable to an ambulant patient setting, which would be the Holy Grail of RHTN therapy.

Chemical Neural Ablation

Therapeutic pharmacological neurolysis has been recognised for over a century and several pharmacological agents are being developed for RSD (see Table 3). Targeted drug delivery is an attractive method offering selective neurolysis and obviating endothelial and deeper vascular damage. Alcohol is an effective neurolytic,⁴⁵ previously used for trigeminal neuralgia,⁴⁶ and, in fact, more than 20 years ago⁴⁷ to treat renovascular hypertension through percutaneous injection into the renal artery adventitia. Botulinum toxin type A (commonly known as Botox®) or type B are responsible for the flaccid paralysis associated with *Clostridium botulinum* poisoning, and have been developed as therapeutic neurolytics to treat muscular dystonias⁴⁸ and spasticity.⁴⁹ Similar neurotoxins have been packaged in magnetic nanoparticles that provide a mechanism for targeted drug delivery when combined with an external magnetic field, and have been successfully applied to cardiac SNS ganglionic plexi to treat atrial fibrillation.⁵⁰ Guanethidine, one of the first anti-hypertensive medications, reduces norepinephrine (NE) levels in pre-synaptic nerve terminals. At higher systemic doses it has been shown to cause selective SNS neurolysis⁵¹ through an immune-mediated mechanism.⁵² The anti-neoplastic vinca alkaloid, vincristine, is well recognised to be neurotoxic, especially to peripheral nerves with systemic application,⁵³ and while this can cause disabling peripheral neuropathies in cancer patients, this medication has been re-tasked for therapeutic usage as an RSD agent, and is the only chemical-based RSD technology that has produced both preclinical and first-in-man data in peer-reviewed publications.^{54–56}

Cryoablation to Achieve Renal Sympathetic Denervation

Cryotherapy, an effective ablation technology, cools target tissue to ≤40°C, which results in intra-cellular ice crystal formation and cell death⁵⁷ and has been used to destroy non-epithelial tissue for

over 50 years.⁵⁸ Cryoablation has become a mainstay for cardiac EP studies, as there is a reduced frequency of vascular complications⁵⁹ and reduced pain⁶⁰ compared with standard RF techniques. Standard cardiac EP cryoablation catheters have been used to determine the safety of this approach in preclinical studies that demonstrated effective RSD with no macroscopic evidence of endovascular thrombi, renal parenchymal or vascular damage and endothelial cell preservation by immunohistochemistry.⁶¹ In a small pilot study in patients with RHTN deemed non-responders to RF RSD, cryoablation caused appreciable BP reductions in all three patients to 6 months post-procedure (>22/4 mmHg ambulatory BP).⁶² This approach is being developed by commercial ventures, including CryoMend Inc. and Cryomedix Inc. (both San Diego, US) although there have been no preclinical or clinical data outputs to date. It is too early to speculate on the long-term potential for cryoablation in RSD and on a cautionary note, higher rates of recurrence after successful index ablation are apparent for certain cardiac arrhythmias compared with RF ablation.⁶⁰

Ionising Radiation Neural Ablation

Radio-ablation is also being developed for endovascular RSD. Although peripheral nerves were initially thought to be relatively radio-resistant, it was established more than 50 years ago that ionising radiation induced neural fibrosis and myelin loss, leading to symptomatic neuropathies in cancer patients treated with radiotherapy.⁶³ Novel, radiation-based therapies that are being developed for RSD include endovascular β -radiation brachytherapy (25–50 Gy delivered by Best Vascular Inc., [Springfield, Virginia] Novoste™ Beta-Cath™ catheter), which has demonstrated effective neural destruction and renal artery safety at 25–50 Gy in swine (n=10) up to 2 months post-procedure,⁶⁴ and stereotactic, non-invasive, robot-assisted, X-radiation radio-surgery (Cyberheart Inc., [Sunnyvale, US] Cyberheart system™), based on the same company's Cyberknife™ system, used to treat solid organ tumours. No preclinical data have been presented to date.

Current Controversies and Future Opportunities **Technical Failure versus Non-responder**

One of the main problems with current application of all RSD technologies is the inability to separate technical failure of the procedure from lack of response of patients to effective RSD. This latter problem could arise because either that renal SNS signalling is not paramount to RHTN in that patient (i.e. other mechanisms are driving the RHTN phenotype) or that the patient's anatomy/physiology is unable to respond to the reduction in SNS signalling (i.e. large vessel stiffening). Furthermore, a purported cumulative effect to RF RSD in terms of BP lowering over 3 years³⁰ may mean that early lack of BP lowering does not reflect lack of either procedural success or response to RSD. This would seriously complicate decision-making regarding 're-do' procedures (clinicaltrials.gov: NCT01834118) or proceeding to other interventional technologies, such as baroreflex activation therapy (BAT)^{65,66} or arterio-venous coupling,⁶⁷ in early non-responders to RSD.⁶⁸ Furthermore, the recent announcement of the failure of Symplicity HTN-3 to meet its primary efficacy end-point at 6 months with a first-generation sequential ablation catheter system may reflect difficulties in demonstrating effective neural destruction, a primary end-point that was too early in the natural history of the response to RSD, effective guideline-driven treatment of RHTN in the placebo-sham arm or that RF RSD was truly ineffective in BP lowering in a cohort of patients that had true RHTN in and out of office.

Further research to determine which patients are suitable/likely to respond to RSD is essential. To date, only baseline BP correlates to the magnitude of BP response to RF RSD across multiple cohorts.^{10,30,31,69,70} Single-unit muscle sympathetic nerve activity is reduced within 3 months of RF RSD and may predict future BP response but this is not established yet.⁷¹ Impaired cardiac baroreflex sensitivity predicts BP response to,⁷² and improves after,⁷³ RF RSD.

More recently, intra-arterial BP response to high-frequency stimulation ([HFS] 20 Hz for 10 seconds) at the renal artery ostium immediately post procedure suggests a potential test of procedural efficacy.⁷⁴ In this study, HFS pre-procedure caused an immediate >15 mmHg increase in BP in all patients that was almost entirely blunted (<6 mmHg) post RF RSD.⁷⁴ Other investigations that have been utilised in subsets of patients include renal NE spillover¹⁰ and single-unit muscle sympathetic nerve activity.⁷¹ However, both techniques are time consuming, require invasive testing pre- and post-procedure and are currently only available in specialist centres with expertise of autonomic function assessment. These concerns highlight the growing importance of collaboration with autonomic neurophysiologists and cardiovascular physiologists to develop the means to accurately phenotype individual patients with respect to the role of the SNS and its many subdivisions in their hypertension. In a similar fashion, the clinician already subjects patients to detailed biochemical and imaging characterisation as a pre-requisite to adrenalectomy for patients with adrenal nodules. Why then should (expensive and invasive) RSD be offered to all patients with RHTN without first determining the involvement of their renal SNS?

Clinical Trials Inadequacies

Criticisms of published RSD clinical trials have been widely propagated^{75–78} and include lack of sham control; non-blinded design; no *per protocol* exclusion of both secondary causes of hypertension and non-adherence to therapy; intermediate soft end-points (often 6 month office BP); and lack of ambulatory BP use as standard for both inclusion to exclude white coat effect, and also as a BP outcome and lack of durability and safety beyond 3 years. Ambulatory BP has been included in more recent small studies in moderate RHTN,^{79,80} and both sham control (clinicaltrials.gov: NCT01418261) and major adverse cardiovascular events as primary end-points (clinicaltrials.gov: NCT01903187) are included in current large international studies but the results from these studies will not be known for many years, so the current use of RSD technologies is based on low numbers of non-high-quality studies. Durability of BP lowering has recently been demonstrated for at least 3 years,³⁰ but concerns about renal nerve regrowth remain⁸¹ although the potential impact of any re-innervation on BP is unclear.³⁰ Reassuringly, denervated renal transplants have preserved functions of solute clearance, electrolyte transport and hormonal function⁸² and RF RSD in moderate to severe CKD is both effective and safe up to 1 year post procedure.³⁹

What is the Best Renal Sympathetic Denervation System?

Currently it is difficult to recommend one RSD technology above and beyond any other, as there are no head-to-head comparisons of intra- or inter-class RSD technologies. The majority of clinical trial experience is with the first-generation RF Symplicity catheter, though as outlined previously methodological and technological

advances in second-generation RF and other non-RF systems give theoretical preference to more recent iterations. A clinical study of four RSD technologies, including one single electrode RF system, two multi-electrode systems and one non-RF system, may help answer this question with respect to BP lowering and procedural and renal artery safety (clinicaltrials.gov: NCT01888315). Notably, it remains unproven whether any technological form of RSD is equivalent (or superior) to guideline-driven pharmacological management of RHTN⁵ and specific trials of this type are not currently under way. Until this is the case, RSD should remain a treatment of last resort for RHTN.

Conclusion

To date, the majority of clinical studies have evaluated the efficacy of RF (and non-RF) RSD in predominantly severe RHTN. However, given that the pathophysiological basis for RSD therapy is based not on BP level but on the recognition that RHTN is associated with elevated central SNS tone, RSD may be an effective treatment for other conditions that exhibit similar elevated central SNS tone, whether renally mediated or not. As such, RF RSD has been evaluated in other systemic conditions and pleiotropic effects of RF RSD have been reported in both systolic⁸³ and diastolic⁸⁴ heart failure,

obstructive sleep apnoea,⁸⁵ glycaemic control in RHTN patients^{85,86} and both supra-ventricular⁷⁴ and ventricular arrhythmias.⁸⁷

With the proliferation of different technologies and devices for RSD, much more rigorous research is required so that clinicians can confidently and fully inform patients with RHTN which is the most efficacious and safe intervention for them, taking into account the individual pathophysiological basis for RHTN and matching that to available technologies or not as is appropriate. The principles that should guide development of and selection of appropriate RSD technologies should include: minimally/entirely non-invasive device; predictability of injury pattern; selectivity for renal nerves; permanent nerve destruction; minimal injury to renal artery and collateral structures; minimal procedural pain; short procedure time; durable modulation of central SNS tone; and BP lowering. The publication of the Simplicity HTN-3 dataset is now critical so that the full implications of this disappointing result can further inform the most appropriate use of this technology and treatment for RHTN and potentially other disorders as well. The hypertension specialist, and patients, should welcome this paradigm shift in the landscape for treatment of RHTN but a cautious approach should be maintained with newer, novel technologies until evidence emerges to support their use. ■

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