Renal Sympathetic Denervation for Treating Resistant Hypertension

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Systemic hypertension represents a significant global concern, because it contributes to vascular and renal morbidity, cardiovascular mortality, and economic burden, hence the impact of hypertension is a major issue in public health worldwide. Improving high blood pressure management is therefore fundamental to influencing clinical outcomes. Despite adherence to multiple available medical therapies, a significant proportion of patients has persistent blood pressure elevation, a condition termed “resistant hypertension”. Renal sympathetic innervations contribute to lack of response of anti-hypertensive drugs through an imbalance of regulatory mechanisms. Renal afferent nerve fibers are responsible for sympathetic activation and contribute to blood pressure homeostasis while afferent signals from the kidneys are integrated at the central nervous system and enhance sympathetic nerve discharge. In this regard, a novel strategy that selectively removes these hypertensive contributors represents a new therapeutic opportunity. Recently, a catheter-based method to induce renal sympathetic denervation has been introduced into daily practice. Clinical evaluation of selective renal sympathetic denervation demonstrated a decrease of renal norepinephrine spillover and renin activity, an increase of renal plasma flow, and has confirmed clinically significant, sustained reductions in blood pressure in patients with resistant hypertension. This review summarizes the available data on the role of sympathetic activation in the pathophysiology of hypertension and the current concepts in transcatheter renal artery ablation with radiofrequency delivery for systemic hypertension. Suggestions regarding targets for future systemic hypertension management are also described. (Circ J 2013; 77: 857–863)

Key Words: Endovascular therapy; Hypertension treatment; Renal denervation; Sympathetic nervous system; Systemic hypertension

Hypertension has a prevalence of 65% in the over 60 age group, affecting nearly 1 billion people worldwide. It is a major risk factor for cardiovascular disease, including stroke, heart and renal failure, and it is responsible for 7 million deaths worldwide annually. Treating high blood pressure is important for prevention of related diseases, such as cerebrovascular disease, ischemic heart disease and renal impairment. Several anti-hypertensive agents are available, and the number of people with systemic hypertension whose blood pressure is under control has increased over the past 2 decades. Nevertheless, among patients with hypertension, only 25–35% can be acknowledged as having reached the desired clinical target, given that there exists a subgroup that is unable to achieve adequate blood pressure monitoring despite the use of multiple medications, dietary and lifestyle modifications. Resistant or refractory arterial hypertension is defined as blood pressure that remains above goal despite concurrent use of 3 or more anti-hypertensive drugs of different classes, including a diuretic, at their maximum or highest tolerated doses. Of note, many patients labeled as having resistant hypertension do not have genuine drug-resistant hypertension; instead, they are non-adherent to therapy or are on an inappropriate regimen. Additional causes of resistant hypertension are renal artery stenosis, volume overload due to progressive renal insufficiency, primary hyperaldosteronism, excessive salt intake, obstructive sleep apnea and, most often, inadequate diuretic therapy. Some rare causes can include pheochromocytoma, Cushing’s syndrome, hyperparathyroidism, and coarctation of the aorta (Table 1).

All these forms of hypertension have a significant neurogenic component that is concomitantly initiated and sustained by activation of the sympathetic system and, in contrast, by inhibition of the parasympathetic counterpart. The role of the sympathetic nervous system in modulating blood pressure has been extensively investigated during the last century, and some drugs have already been proven to efficiently act on adrenergic apparatus such as α-metildopa in the 1950s, β-blockers in the 1960s, α-blockers in the 1970s, angiotensin-convertase enzyme inhibitors in the 1980s, and moxonidine in the 1990s. None of them, however, has turned out to be as effective as...
renal denervation. The proof of concept for applying such a therapeutic strategy mainly derives from the assumption that sympathetic nerves enter the kidneys in the walls of the renal arteries, thus affecting renal function in 3 different ways: (1) increasing the renin secretion rate through the β1-adrenergic receptors; (2) enhancing sodium and water reabsorption through α2B-adrenergic receptors; and (3) inducing renal vasoconstriction with renal blood flow and glomerular flow rate reductions through α1A-adrenergic receptors (Figure).12

These sympatho-excitatory effects have been observed in several experimental models in response to kidney injury, leading to the assumption that sympathetic hyperactivation progressively affects sodium balance and leads to conditions such as congestive heart failure and arterial hypertension.13

but also determines target-organ damage such as left ventricular hypertrophy14 and progressive renal damage.15

Sympathetic-mediated peripheral vasoconstriction is due to stimulation of post-synaptic α1- and α2-adrenoceptors in normal subjects as well as in heart failure,16,17 and sympathetic vasoconstriction has been documented in coronary circulation.18 Therapeutic renal denervation has been explored in preclinical models19 and in humans20 since the 1950s, when surgical renal denervation was shown to be a highly effective treatment for resistant hypertension in the clinical setting. Unfortunately, the procedure was abandoned because of intolerable side-effects, but gave rise to other promising surgical techniques, such as carotid baroreceptor surgery for resistant hypertension, which showed encouraging results.21

Recently, percutaneous renal denervation has emerged as a potential mini-invasive strategy to treat resistant hypertension.22 It is a localized procedure, minimally invasive, and has no systemic side-effects. Moreover, procedure and recovery times are very short compared to the surgical procedure.23 The main studies of renal denervation are the Symplicity HTN-124 and the randomized controlled Symplicity HTN-2 trial.25 In both trials, this approach was shown to successfully reduce blood pressure, without serious adverse events in patients with resistant hypertension.

This review outlines the pathophysiological background of hypertension, describes the past and the present of renal denervation, starting from preclinical studies to the latest study in humans and considers several future potential applications.
Preclinical Studies

During the last century, advances in the understanding of the physiology of renal vasculature have highlighted the potential for transluminal ablation in treating hypertension through renal arteries denervation, which has recently been investigated with regard to the safety and feasibility of dedicated therapeutic equipment in small and large animal models, respectively. The function of the kidney when deprived of any sympathetic influences to and from the organ in animals undergoing bilateral nephrectomy and auto-implantation of their kidneys results in significant diuresis, most likely due to a readjustment of the pressure natriuresis response. In a canine model, stimulation of renal sympathetic nerves causes hypertension, in part because of a reduction in renal blood flow. This aspect has been further addressed in a model of unilateral renal denervation in dogs treated by rapid injection of 6-hydroxydopamine into the renal artery with simultaneous collection of the venous effluents to avoid systemic effects. Preclinical experiments using renal denervation as the therapeutic strategy have included numerous disease states, such as hypertension, myocardial infarction, heart failure, and chronic kidney disease. Renal denervation decreases blood pressure in deoxycorticosterone acetate-treated miniature swine with established hypertension, and attenuates both sodium retention and systemic hypertension associated with obesity in dogs. Moreover, augmentation of renal sympathetic activity has been studied in spontaneously hypertensive rats, in which the development of hypertension is delayed and the severity is attenuated by prior bilateral renal sympathetic denervation. The long-term effects of renal denervation have also been addressed in rats, showing that increased renal sympathetic nerve activity might contribute to the progression of heart failure after myocardial infarction, because renal denervation reduces left ventricular filling pressure and improves left ventricular function after infarction, probably through restoring impaired natriuresis. Kidney perfusion and vascular resistance have represented recent areas of investigation, shedding new light on the comprehension of the pathophysiology of the cardio-renal syndrome and its treatment. In this regard, renal denervation abolishes hypertension in low-birth-weight offspring from pregnant rats with reduced uterine perfusion, while another report indicated that angiotensin II is likely to facilitate the release of non-epinephrine from renal sympathetic nerve terminals through a presynaptic site of action in a rat model of essential hypertension.

Of note, renal denervation has been performed in a swine model to characterize the vascular safety and healing response after renal denervation. This procedure, via ablation of sympathetic nerves through a radiofrequency (RF)-based catheter system was not associated with clinically significant adverse renal findings 6 months after the procedure. At the molecular level, a recent study showed that renal denervation significantly decreased collagen content and the mRNA expression of collagen I and III, in addition to altering the expression of fetal gene programming in rats undergoing experimental aortic re-gurgitation, with the final effect of preventing albuminuria and glomerular podocyte injury when added to an angiotensin II type 1 receptor blocker, providing new insights into the management of cardio-renal syndrome. Consistently, these studies have exploited several aspects of renal denervation physiology and showed that the renal sympathetic system plays a pivotal role in determining hypertension, heart failure, and chronic kidney disease. Taken together, these experiments emphasize the potential therapeutic value of renal denervation.

Surgical Sympathetic Denervation

Unselective sympatholytic surgery has been practiced since the 1930s to treat severe hypertension when oral pharmacological therapies and device-based techniques were not available. The surgical approaches were mainly thoracic, abdominal, or pelvic in order to achieve radical sympathetic denervation. These methods, however, were associated with high perioperative morbidity and mortality and long-term complications, including severe orthostatic hypotension, orthostatic tachycardia, palpitations, breathlessness, anhidrosis, cold hands, in addition to bladder dysfunction, intestinal disturbances, loss of ejaculation, sexual dysfunction, thoracic duct injuries, and atelectasis. Furthermore, blood pressure reduction was inconsistent and observed in only 50% of cases, and the procedure was abandoned in the mid-late 1960s when effective and much better-tolerated orally active anti-hypertensive drugs became available.

Catheter-Based Renal Denervation in Humans

In the first decade of the 2000s endovascular RF ablation of renal sympathetic nerves was developed and the first proof-of-principle, non-randomized trial of therapeutic renal sympathetic denervation in patients with resistant hypertension was reported by Krum et al. That trial analyzed data from 45 patients treated with renal denervation. After only 1 month systolic and diastolic blood pressure (SBP and DBP) had both decreased significantly, by 14 mmHg and 10 mmHg, respectively, and by 12-month follow-up the decreases were 27 mmHg and 17 mmHg. That study provided the first evidence that ablation-induced renal denervation is safe. Several concerns, however, must be explored. The study was limited by lack of a control group, suboptimal candidate exclusion criteria and small patient number. These findings suggested that continued research into therapeutic renal-nerve ablation for the treatment of hypertension is of interest. The logical consequence was to continue the trial, leading to the Symplicity HTN-1 Trial. That study was indeed built upon the previous cohort by increasing the patient numbers and including follow-up data up to 24 months. Study methodology remained non-randomized with 153 treated patients. Baseline data included mean office blood pressure of 176±17/98±15 mmHg, mean of 5 anti-hypertensive medications, and an estimated glomerular filtration rate of 83±20 ml·min⁻¹·1.73 m². The median time from first to last RF energy ablation was 38 min. The procedure was without complications in 97% of patients (149 of 153). The 4 acute procedural complications included 3 groin pseudoaneurysms and 1 renal arterial dissection, all managed without further sequelae. Post-procedure office blood pressure assessments were reduced by 20/10 mmHg, 24/11 mmHg, 25/11 mmHg, 23/11 mmHg, 26/14 mmHg, and 32/14 mmHg at 1, 3, 6, 12, 18, and 24 months, respectively. In conclusion, in patients with resistant hypertension, catheter-based renal sympathetic denervation resulted in a substantial reduction in blood pressure sustained to ≥2 years of follow-up, without significant adverse events. Weaknesses in this trial are similar to that of the first proof-of-principle trial. It lacked a proper control group, it was small, the group of patients recruited was not clearly defined, and predictors of blood pressure response had not been identified. Therefore, regression to the mean needs to be considered together with additional statistic factors in results interpretation.
The expanded 2-year cohort data were presented for the first time at the 24th Annual Transcatheter Cardiovascular Therapeutics (TCT 2012) scientific symposium. Responder rates (defined as a 10 mmHg reduction) among patients completing follow-up increased from 69% at 1 month to 82% at 24 months. Safety follow-up at 24 months demonstrated stable renal function; furthermore, endoluminal RF delivery induced fibrosis and no significant decline in kidney function were reported at 12 months. In conclusion, at 12 months of follow-up, the Symplicity HTN-2 trial demonstrates safety and continued benefit of renal denervation for the management of uncontrolled, treatment-resistant hypertension. In that study there were some limitations, such as lack of 24-h blood pressure monitoring and no blinding of patients nor dedicated staff to assess blood pressure. These methodological shortcomings will be addressed directly in the ongoing Symplicity HTN-3 trial that is currently recruiting patients affected by uncontrolled hypertension (NCT01418261 at http://clinicaltrials.gov).43 The Symplicity HTN-3 study is a multi-center, prospective, single-blind, randomized, controlled study of the safety and effectiveness of renal denervation in subjects affected by uncontrolled hypertension and will involve more than 500 patients evaluated in 87 centers in the USA. Primary outcomes to be evaluated will be change in office SBP at 6 months and incidence of major adverse events through 1-month after randomization. A secondary outcome is average 24-h ambulatory blood pressure. Interestingly, much greater emphasis will be placed on use of an aldosterone antagonist, addressing its safety, effectiveness and tolerability. Effects of renal denervation on blood pressure reduction in the Symplicity HTN trials are listed in Table 2.

Limitations of Transcatheter RF Ablation

Although methodological limitations have been encountered for almost each study on transcatheter renal denervation described so far, it should be taken into account that the major point of strength for introducing the next trial and for reinforcing the assumption that renal denervation is useful, safe, and effective in hypertension management, mostly for those patients suffering hypertension while unresponsive to >3 blood pressure medications. In addition, a recent work has underlined the lack of long-term morphological follow-up of the renal artery and kidney after RF renal denervation. Reports on kidney injury are still incomplete;44,45 data on damage to the renal artery including stenosis and/or aneurysm are not available; the follow-up is still short, and no one can be absolutely sure that 5 or 10 years later a patient will not develop one of these complications; furthermore, endoluminal RF delivery induced fibrosis whereas they did not differ from baseline in the control group. Between-group differences in blood pressure at 6 months were 33/11 mmHg (P<0.0001). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in SBP ≥10 mmHg, compared to 18 (35%) of 51 control patients (P<0.0001).

One-year results from the Symplicity HTN-2, were reported by Esler et al.42 These data showed that patients who initially received treatment with the Symplicity renal denervation system sustained a significant drop in blood pressure (–28/–10 mmHg; P<0.001) compared to baseline at 12 months; these 12-month results demonstrated preservation of the benefits already seen at 6-month follow up (–32/–12 mmHg). No device-related serious adverse events, no late vascular complications, and no significant decline in kidney function were reported at 12 months. Furthermore, 6-month results for 35 patients in the control group who received renal denervation after the primary endpoint was assessed at 6 months following randomization (referred to as the cross-over group). The cross-over group also had a significant drop in blood pressure 6 months after the renal denervation procedure (–24/–8 mmHg; P<0.001). This decrease in blood pressure was similar to the blood pressure reduction in the initial treatment arm at 6 months. In conclusion, at 12 months of follow-up, the Symplicity HTN-2 trial demonstrates safety and continued benefit of renal denervation used for the management of uncontrolled, treatment-resistant hypertension. In that study there were some limitations, such as lack of 24-h blood pressure monitoring and no blinding of patients nor dedicated staff to assess blood pressure. These methodological shortcomings will be addressed directly in the ongoing Symplicity HTN-3 trial that is currently recruiting patients affected by uncontrolled hypertension (NCT01418261 at http://clinicaltrials.gov).43 The Symplicity HTN-3 study is a multi-center, prospective, single-blind, randomized, controlled study of the safety and effectiveness of renal denervation in subjects affected by uncontrolled hypertension and will involve more than 500 patients evaluated in 87 centers in the USA. Primary outcomes to be evaluated will be change in office SBP at 6 months and incidence of major adverse events through 1-month after randomization. A secondary outcome is average 24-h ambulatory blood pressure. Interestingly, much greater emphasis will be placed on use of an aldosterone antagonist, addressing its safety, effectiveness and tolerability. Effects of renal denervation on blood pressure reduction in the Symplicity HTN trials are listed in Table 2.

### Table 2. Effects of Renal Denervation on BP Reduction in Symplicity HTN Trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>Size (no.)</th>
<th>Mean baseline (mmHg)</th>
<th>Decrease in BP 1 month (mmHg)</th>
<th>Decrease in BP 3 months (mmHg)</th>
<th>Decrease in BP 6 months (mmHg)</th>
<th>Decrease in BP 12 months (mmHg)</th>
<th>Decrease in BP 24 months (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SBP</td>
<td>DBP</td>
<td>SBP</td>
<td>DBP</td>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>Symplicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN-3[43]</td>
<td>530</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

BP, blood pressure; DBP, diastolic blood pressure; HTN, hypertension; ND, not detected; SBP, systolic blood pressure.
of the arterial wall in animal studies, and this iatrogenic condi-
tion can determine fragility of the artery and contribute to the
development of stenosis and/or aneurysm. In spite of some pro-
cedural complications, mainly restricted to infrequent he-
matomas at the access site to the femoral artery (approximate-
ly 2% incidence) and 2 reported instances of renal artery dis-
section (<1% in overall experience) that needed renal artery
stenting, percutaneous renal denervation is a safe procedure.
It is noteworthy that inhibition of the sympathetic nervous
system might be not the only mechanism underlying the anti-
hypertensive effect of renal denervation. Although the Sym-
plicity HTN-1 trial provided direct measurements in 10 pa-
tients, such as a 47% decrease in renal norepinephrine spillover
from baseline to 15–30 days after the procedure, 24 while Schlaich
et al found a decrease in whole-body spillover of norepi-
 nephrine and muscle sympathetic nerve activity 1 month after
the procedure in a single patient, 25 there is still the urgent need to
design future trials that consider the effective response of the
sympathetic nervous activity in a randomized and blinded fash-
ion, for instance by measuring changes in circulating or uri-
inary catecholamines, microneurography, quantifying the renal
spillover of catecholamines, or by assessing heart rate vari-
ability. Moreover, the role of the cellular population of the in-
tima and media layers 46 should be addressed, because endo-
thelial cells and vascular smooth muscle cells of the inner
tunica of the renal artery could play divergent roles, such as
proliferation, secretion or de-differentiation, when exposed to
direct injury; these effects could partially explain the observed
changes in peripheral resistance attributed to peripheral arte-
riolar vasodilatation (functional) or vessel (structural) remodel-
ing. Additional studies should clarify to what extent changes in
the circulating volume, and sodium and fluid homeostasis
determine the hemodynamic mechanisms underlying blood
pressure reduction. It should be noted that all the afore-men-
tioned studies are missing a proper sham-operated group, which
would have provided double-blinding and reduced potential
bias. It is well known that the prevalence of primary aldoste-
ironism, sleep apnea, and white-coat hypertension is increased
in resistant hypertension. Therefore the per-protocol exclusion
of secondary and white-coat hypertension would have been
more appropriate, but luckily these points will be extensively
addressed in the ongoing Symplicity HTN-3 study. 43 Finally,
as highlighted by the Symplicity HTN-1 investigators, efferent
nerves anatomically regrow over a period of months to years
after renal denervation, but without consistent demonstration
of functional reinnervation; this remains an open issue on the
durability of the blood pressure-lowering effect.

**Future of the Treatment of Hypertension**

Optimization of pharmacologic and non-drug-based treatment
of hypertension remains one of the biggest challenges in the
clinical scenario. The development and implementation of safe
and effective anti-hypertensive drugs from various classes have
been enormous and continue to prevent and reduce cardiovas-
cular morbidity and mortality worldwide. Current guidelines
for treatment of hypertension typically relegate anti-adrener-
gic drugs to the third or fourth tier, although the sympathetic
nervous system plays a pivotal role in the pathogenesis of
hypertension. Therefore, future developments are directed tow-
ard other pharmacologic agents and in the search for improve-
ments in currently adopted device-based techniques. Among
the latter, renal denervation has been proven to be the safest
and the most effective therapeutic approach for curing hyper-
tension and several devices have been approved for this pro-
cedure (Table 3); other biomedical tools, however, are avail-
able such as an implantable device to reduce blood pressure
by stimulating the arterial baroreceptors; device-guided respi-
ration that assists with slow breathing; use of continuous pos-
itive airway pressure devices in hypertensive patients with ob-
structive sleep apnea; direct electrical stimulation of brain
regions to change blood pressure reassessment; devices stimu-
lating the arterial baroreceptors; and surgical neurovascular
depression of the brainstem to overcome presumed vascular
compression of bulbar regions that control sympathetic out-
flow and blood pressure. In contrast, several brand new phar-
macologic agents are currently under investigation with regard
to providing additional choices in the field of molecular ther-
apy for hypertension. These novel drugs are all in phases 2 or
3 of clinical experimentation studies. In particular, some class-
es can be identified regarding their mechanisms of action: (1)
dual vasopeptidase inhibitors; (2) dual-acting angiotensin re-
ceptor- neprilysin inhibitors; (3) aldosterone synthase inhibi-
tors; (4) endothelin antagonists; (5) 2 angiotensin-based vac-
cines; (6) dual angiotensin type 1 receptor/Endothelin type A
antagonist; and (7) inhibitors or breakers of advanced glyca-
tion end-products, which target the molecular components of
the aortic wall responsible for arterial stiffening. In addition,
novel drugs and molecules are at this moment in preclinical
development: (1) nitric oxide donors; (2) renin-prorenin block-
er; (3) angiotensin II-converting enzyme-2 activator; (4) ami-
nopeptidase-A inhibitor; and (5) dual AT1R blocker and par-
tial peroxisome proliferator-activated receptor-γ agonist. All
of them act on newly discovered cell-signaling pathways or
recently identified pathophysiological mechanisms, and their
variety reflects both the growing interest from pharmaceutical

### Table 3. Principal Equipment for Renal Denervation

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Clinical randomized trials</th>
<th>Technical features</th>
<th>Catheter caliber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symplicity Catheter System</td>
<td>Medtronic</td>
<td>Yes</td>
<td>Flexible catheter with a single electrode tip for RF energy delivery.</td>
<td>6F</td>
</tr>
<tr>
<td>EnligHTN Multi Electrode Renal Denervation System</td>
<td>St. Jude Medical</td>
<td>No</td>
<td>This denervation catheter is a monopolar multi-point electrode RF ablation catheter.</td>
<td>8F</td>
</tr>
<tr>
<td>OneShot Renal Denervation System</td>
<td>Covidien</td>
<td>No</td>
<td>Over-the-wire balloon RF catheter with embedded electrodes.</td>
<td>6F–7F</td>
</tr>
<tr>
<td>Paradise Renal Denervation System</td>
<td>ReCor Medical</td>
<td>No</td>
<td>Angioplasty catheter with a cylindrical transducer that emits US energy circumferentially.</td>
<td>6F</td>
</tr>
<tr>
<td>V2 Renal Denervation System</td>
<td>Vessix Vascular</td>
<td>No</td>
<td>Over-the-wire balloon RF catheter with embedded electrodes.</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, not detected; RF, radiofrequency; US, ultrasound.
industries, and also the complexity of drug development to treat hypertension. Finally, future research needs to investigate whether renal denervation can be applied in milder forms of hypertension, for non-compliant patients, and in several other diseases involving raised sympathetic activity such as left ventricular hypertrophy, chronic heart failure and cardio-renal disorders (Table 4).

Conclusions
Sympathetic renal hyperactivity plays a fundamental role in the pathophysiology of systemic hypertension and in its progression towards organ damage. As a result, a succession of therapeutic approaches has targeted the sympathetic nervous system to modulate hypertension, with varying success. Surgical renal denervation, although highly effective in reducing blood pressure, was associated with a significant amount of side-effects and was rapidly replaced by better-tolerated medical therapy. Current pharmacologic strategies attempting to control blood pressure in patients with resistant hypertension are not always effective. The rapid progress in catheter-based technologies occurring within the last 20 years facilitated the development of percutaneous catheter-based renal artery ablation that has emerged as a new approach to achieving blood pressure reduction in patients with resistant hypertension. Current results from the use of catheter-based renal denervation suggest significant reduction in blood pressure while maintaining the safety and efficacy of the method. Furthermore, as many as 90% of the treated patients respond to the procedure. Transcatheter renal denervation is associated with procedural complications in only 2.61% of cases. Available clinical data on percutaneous catheter-based renal artery ablation for treatment of resistant hypertension have demonstrated a clinical benefit, but further larger studies are required for establishing long-term maintenance of positive results, as well as providing clear indicators and precise parameters of successful renal artery ablation.

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Renal RF Ablation of Hypertension


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