Review paper

Renal denervation: can we press the "ON" button again in 2020?

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Abstract

In December 2018, an article summarizing available results of randomized studies on renal denervation (RDN), entitled "Renal denervation: can we press the ON button again?" was published in the *Advances in Interventional Cardiology*. Since then, several positive reports, including SPYRAL HTN OFF-MED Pivotal trial have been presented. In the current review the authors discuss the latest data on RDN in arterial hypertension treatment and try to answer the burning question: can we press the ON button again in 2020? The results of recently published studies potentially justify new recommendations for the use of RDN in clinical practice in appropriately selected patients in the new hypertension guidelines. The current review also summarizes the results of trials on RDN applied in another potential indication – atrial fibrillation. Six most important, prospective, randomized trials assessing RDN as adjunct therapy to pulmonary vein isolation for treatment of atrial fibrillation were discussed. In 5 studies, patients had uncontrolled BP despite treatment with three antihypertensive agents. The ratio for recurrence of atrial fibrillation for pulmonary vein isolation with RDN procedure was reduced by 57% as compared to pulmonary vein isolation (PVI) alone. BP was also reduced significantly after RDN in this subset of patients. Further multicenter studies involving standardized PVI and RDN procedures are needed.

Key words: renal denervation, atrial fibrillation, hypertension.

Introduction

In December 2018, in *Advances in Interventional Cardiology*, we published an article summarizing available results of randomized studies on renal denervation (RDN), entitled "Renal denervation: can we press the ON button again?" [1]. Positive results of small pilot studies with new-generation devices (SPYRAL HTN ON-MED, SPYRAL HTN OFF-MED and RADIANCE-HTN SOLO) were not available at the time of writing the European hypertension guidelines and consequently the European Society of Cardiology/European Society of Hypertension joined guidelines consensus recommended to use this procedure only in clinical trials to provide further evidence on safety and efficacy in a larger set of patients [2].

Since then, several reports, including SPYRAL HTN-OFF MED Pivotal trial have been published [3]. In the current review we discuss the latest data on RDN in arterial hypertension (HTN) treatment and try to answer the burning question: can we press the ON button again in 2020? We also summarize the results of studies on RDN applied in another potential indication – atrial fibrillation (AF).

Renal denervation in arterial hypertension

Randomized sham-controlled trials

In SPYRAL HTN-OFF MED Pivotal trial, recently published in Lancet, 331 patients with uncontrolled HTN (inclusion criteria presented in Table I), off antihypertensive medications, were randomized 1 : 1 to RDN or sham treatment. The SPYRAL HTN OFF MED Pivotal trial utilized a Bayesian adaptive design that efficiently leverages data from the SPYRAL HTN OFF MED Pilot trial (published in 2018) to support the Pivotal results.

The RDN procedure was performed using four-electrode Spyral catheter. In each center, only one dedicated operator performed the procedures to minimize procedural variability. The applications were done within the

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Table I. The results of prospective, randomized trials and registries assessing the effects of renal denervation on hypertension treatment published since 2018

Study		SPYRAL-HTN OFF MED [3]	RADIANCE-HTN SOLO [4]-extension	REDUCE HTN: REINFORCE [5]	Mahfoud *et al.* [6]	Global Symplicity Registry [7]
Type of study		RCT	RCT – extended follow up	RCT	Non-randomized, single-arm, open-label	Global registry
Device used		Multi-electrode unipolar radiofrequency catheter	Ultrasound-based catheter	Bipolar radiofrequency catheter	Alcohol-mediated renal denervation	Uni-electrode unipolar radiofrequency catheter
Main inclusion criteria of BP		Office SBP 150–179 mm Hg AND DBP ≥ 90 mm Hg AND 24-hour ambulatory SBP 140–169 mm Hg off antihypertensive drugs	Ambulatory 24-hour SBP 135–169 mm Hg AND 24-hour DBP 85–104 mm Hg, on 1–3 antihypertensive drugs initiated 2–5 months after RDN/sham	Office SBP 150–180 mm Hg AND 24-hour ambulatory SBP 140–170 mm Hg off antihypertensive drugs	Office SBP of ≥ 150, DBP/ ≥ 85 mm Hg AND 24-h ambulatory SBP of ≥ 135 mm Hg on at least 3 antihypertensive drugs including diuretic	Office SBP ≥ 150 mm Hg AND 24 h ambulatory SBP ≥ 135 mm Hg
No. of patients/controls included		166/165	74/72	34/17	45/–	1742/–
Sham treatment?/off meds?		Yes/yes	Yes/no	Yes/yes	No/no	No/no
Follow-up period		3 months	6 months	8 weeks	6 months	3 years
BP lowering effect of RDN/sham [mm Hg]						
Office	RDN: SBP/DBP	–9.2/–5.1	–18.2/–10.1	–5.2/–2.5	–18/–10	–16.5/NA
	Sham: SBP/DBP	–2.5/–1.0	–15.9/–9.5	–7.1/–4.8	ND	ND
ABPM	RDN: 24-h SBP/DBP	–4.7/–3.7	–16.5/–9.7	–5.3/–2.6	–11/–7	–8.0/NA
	Sham: 24-h SBP/DBP	–0.6/–0.8	–14.9/–9.4	–8.5/–4.6	ND	ND

BP – blood pressure, SBP – systolic blood pressure, DPB – diastolic blood pressure, NA – not available, ND – not done, RCT – randomized controlled trial.

renal artery main trunks, their distal branches, as well as in additional renal arteries, provided that the minimal vessel diameter was at least 3mm. In the RDN group, the mean number of applications was 46.9 (18.3 in main arteries and 28.6 in branch vessels).

Moreover, blood and urine tests were assessed, with patients' awareness, at baseline and 3 months, for checking the absence of antihypertensive drug metabolites. At baseline, no antihypertensive medications were detected in 91% of the RDN group and 87% of the sham group. At 3 months, excluding patients who had to be treated due to increased blood pressure (BP), 91% and 95% of the subjects, respectively, remained off medications.

After 3 months, 24-hour systolic blood pressure (SBP) decreased by 4.7 mm Hg in RDN as compared to 0.6 mm Hg in the sham group ($p < 0.0005$). In office measurements, the SBP reductions were 9.2 vs 2.5 mm Hg, respectively ($p < 0.0001$). The treatment difference between the 2 groups for 24-h SBP was 3.9 mm Hg and for office SBP was 6.5 mm Hg and fulfilled prespecified criteria for RDN superiority with more than 0.999 probability. Interestingly, both systolic and diastolic blood pressure (DBP) decreases observed after RDN were consistent across the whole day. No major device-related or procedural-related safety events occurred up to 3 months, confirming the safety of RDN with the use of a new generation multi-electrode catheter.

In May 2019, 6-month results of RADIANCE-HTN SOLO trial were published in Circulation [4]. Briefly, RADIANCE-HTN SOLO was a multicenter sham-controlled trial including 146 patients with combined systolic–diastolic HTN after a 4-week discontinuation of up to 2 antihypertensive medications. Patients were assigned 1 : 1 to ultrasound RDN or sham treatment in a 1 : 1 fashion. After 2 months, the reduction in daytime ambulatory SBP was greater with RDN than with the sham procedure (–8.5 vs. –2.2 mm Hg, respectively). The primary endpoint – baseline-adjusted difference between groups (–6.3 mm Hg) was met and the results were published in 2018 in *Lancet* [5].

Between 2 and 5 months after interventional treatment (RDN vs. sham), if monthly measured home BP was elevated (at least 135/85 mm Hg), a standardized antihypertensive treatment was initiated, consisting of the sequential addition of amlodipine (5 mg/day), a standard dose of an angiotensin-converting enzyme inhibitor

or angiotensin receptor blocker, and hydrochlorothiazide (12.5 mg/day). This treatment might be titrated, if needed, to 25 mg of hydrochlorothiazide and 10 mg of amlodipine (10 mg/day). A total of 69/74 RDN patients and 71/72 sham patients completed the 6-month ambulatory BP measurement. At 6 months, 65.2% of patients in the RDN group were treated with antihypertensive treatment as compared to 84.5% in the sham group (p = 0.008). The average number of antihypertensive medications and average defined daily doses were less in the RDN than in the sham group (0.9 vs. 1.3, p = 0.01 and 1.4 vs. 2.0, p = 0.018; respectively). Despite less intensive antihypertensive treatment, RDN reduced daytime ambulatory SBP to a greater extent than sham (–18.1 vs. –15.6 mm Hg, respectively; the difference adjusted for baseline BP and number of medications: –4.3 mm Hg, p = 0.024). There were no major adverse events in either group through 6 months.

Another study, published in JACC Cardiovascular Interventions in February 2020, brought surprising results [5]. The REDUCE HTN:REINFORCE (Renal Denervation Using the Vessix Renal Denervation System for the Treatment of Hypertension) was a randomized, sham-controlled multicenter trial with bipolar radiofrequency multi-electrode Vessix system. Patients with office SBP of 150 to 180 mm Hg and average 24-h ambulatory SBP of 135 to 170 mm Hg after medication washout underwent RDN or a sham procedure. The planned outcome was an 8-week change in 24-h ambulatory SBP. Enrollment was terminated for apparent futility before a sufficient sample for powered efficacy comparisons was enrolled. At 8 weeks, mean 24-h SBP reductions for the RDN and sham groups were –5.3 mm Hg and –8.5 mm Hg, respectively (p = ns). Enrollment was discontinued, but observation continued as planned for patients already enrolled and antihypertensive medications could then be added. Interestingly, at 6 months, decreases in SBP were greater for the RDN group, yielding between-group differences of –7.2 mm Hg for 24-h SBP and –11.4 mm Hg for office SBP. A greater proportion of patients in the RDN arm achieved an office SBP below 140 mm Hg (52% vs. 12%; p = 0.0061) despite the fact that a similar number of patients, roughly 50%, were taking medications in each arm of the trial. Notably, the reduction in BP was sustained between the 6- and 12-month time points, suggesting a durable effect of the procedure.

The authors postulated two potential reasons for delayed response to denervation. First, that RDN does not immediately interrupt systemic sympathetic efferent activity but selectively ablates sympathetic efferent signals to the kidneys. In consequence, the impact of kidneys on renal afferent fibers modifying central regulation is delayed. Second, that the medications might have an additional positive impact on BP decrease achieved with denervation. The efficacy of drugs that work through vasodilation or diuresis can be limited by the increased sympathetic activity, so the sympathoinhibitory effects of RDN might augment the BP-lowering effects of these agents.

Non-randomized studies and registries

In the last weeks, the results of the study evaluating the safety and efficacy of new RDN technology became available [6]. In this study, a novel catheter system (the Peregrine System Infusion Catheter) for the infusion of dehydrated alcohol as a neurolytic agent into the renal periarterial space was used. Forty-five patients with uncontrolled HTN on at least 3 antihypertensive medications underwent bilateral RDN. Mean 24-h ambulatory BP reduction at 6 months versus baseline was 11 mm Hg for systolic and 7 mm Hg for DBP (p < 0.001 for both). Office SBP was reduced by 18/10 mm Hg at 6 months (p < 0.001 for both). Two patients had periprocedural access-site pseudoaneurysms, no other adverse events occurred within 1 month. The ongoing, sham-controlled, randomized, blinded TARGET BP OFF MED and TARGET BP I clinical trials will provide further data with regard to safety and efficacy of this technology.

Global Symplicity Registry

The Global SYMPLICITY Registry is a prospective, open-label registry conducted at 196 sites worldwide in hypertensive patients receiving RDN treatment. The long-term outcomes of 3-year follow-up were published in the *European Heart Journal* [7]. Among 2237 patients enrolled and treated with the SYMPLICITY Flex catheter, 1742 were eligible for follow-up at 3 years. SBP reduction after RDN was sustained over 3 years, including decreases in both office (–16.5 ±28.6 mm Hg, p < 0.001) and 24-h ambulatory SBP (–8.0 ±20.0 mm Hg; p < 0.001). The impact of RDN on BP reduction was more pronounced in patients with severe resistant hypertension (with baseline office SBP ≥ 160 and ABPM SBP ≥ 135 mm Hg on ≥ 3 drugs). In this group of patients, the SBP was reduced after 3 years by 26.7 mm Hg (in office) and 12.4 mm Hg (in ABPM measurement). In multivariable analysis, higher baseline SBP was consistently associated with BP decrease at 12, 24 and 36 months after RDN.

The recent meta-analyses of sham-controlled trials

Before SPYRAL HTN-OFF MED Pivotal trial results were presented, two major meta-analyses were published in 2019-2020 assessing the efficacy of RDN in arterial hypertension. Both analyses, including almost one thousand patients, combined the results of 6 randomized sham-controlled trials, 3 of them used the first-generation device (including the largest SYMPLICITY HNT-3) [8, 9]. Both reports confirmed a statistically significant difference in 24-hour and office SBP reduction as compared to the sham procedure (weighted mean differences

–3.6 mm Hg, $p < 0.001$ and –5.5 mm Hg, $p < 0.001$; respectively). Of note, further analysis demonstrated that the second-generation devices were more effective in SBP reduction than the first-generation ones.

Renal denervation in atrial fibrillation

Hypertension is an important risk factor for developing and maintaining atrial fibrillation (AF). Incidence of AF increases with left ventricular hypertrophy, coronary heart disease, and heart failure, all consequences of poorly controlled hypertension. Pathophysiologically, the imbalance of the sympathetic and vagal nervous system plays an important role in the development and progression of both: AF and HTN [10, 11].

The potential for the antiarrhythmic effect of RDN is based on reduced systemic sympathetic tone what was demonstrated by a decrease in norepinephrine spillover and muscle-sympathetic nerve activity [12].

It is known that acute and chronic BP elevation can increase atrial stretching and dilation (atrial substrate), resulting in deleterious atrial electrical consequences that promote arrythmias. As the heart is densely innervated by autonomic nerve fibers, adrenergic activation may therefore play a role as a trigger on this vulnerable atrial substrate and induce arrythmias including AF [10, 11].

Pulmonary vein isolation (PVI) is an established treatment for symptomatic both paroxysmal and persistent AF, however the effectiveness after a single procedure is reported to be suboptimal. Once PVI has been achieved, the dominant initiating source has been eliminated. However, in patients with substantial pathology in the atrial substrate, additional intervention might be required to maximize antiarrhythmic response since sustained BP elevation will less likely have an impact on the triggers that arise from the pulmonary veins. It is known that one of these interventions is an optimization of BP control what might play a considerable role at the substrate level of the atria in preventing the development or AF recurrence. It was therefore reasoned, first in experimental, and subsequently in the human studies, that RDN could influence the recurrence rate of AF after PVI as the ablation of afferent renal nervous input decreases central sympathetic output, which might attenuate autonomic triggers of AF in addition to improved BP control [10, 11].

Preclinical research indicated several potential atrial antiarrhythmic effects of RDN. In experimental studies RDN was associated with a decreased inducibility and complexity of AF, improved ventricular rate control, reduced shortening of the atrial refractory period, less neurohormonal activation and fewer atrial fibrosis were observed [13–15]. Given this foundation of cardiac effects of RDN, a small, pilot, randomized trial was conducted involving 27 patients with paroxysmal or persistent AF and resistant hypertension [16]. The patients who underwent RDN had a lower rate of AF recurrences, with 69% of them free from AF at 1 year. This important prospective pilot study proved that RDN had a positive impact on AF recurrence in hypertensive patients with refractory AF who also underwent PVI. Also RDN resulted in sustained improvement in systolic and diastolic BP control over 1 year of follow-up in this group of patients [16].

On the basis of encouraging experimental data and results of the pilot study, next bigger randomized, prospective trials have been conducted to further investigate the effects of PVI and RDN in patients with AF and concomitant resistant or uncontrolled hypertension [17–21].

Six most important, prospective, randomized trials assessing RDN as adjunct therapy to PVI for treatment of AF are presented in Table II [16–21]. In 2020, Ukena et al. published the meta-analysis of the above-mentioned trials [10]. The meta-analysis included a total of 689 patients with hypertension and symptomatic AF. In five studies, patients had uncontrolled BP despite treatment with three antihypertensive agents. PVI was performed with irrigated radio-frequency catheters in 387 patients, and in 302 with cryoballoon. Cardiac ablation catheters were used for RDN in 78% of all cases. In the remaining 22%, RDN was performed using a designated, nonirrigated radio-frequency catheter system. After 12 months, the mean odds ratio for recurrence of atrial fibrillation for PVI with RDN compared with PVI alone was 0.43 (95% confidence interval 0.32–0.59). After RDN, BP was reduced significantly whereas no changes were reported in the PVI-only groups. No relevant complications associated to RDN were documented. Further multicenter studies involving standardized PVI and RDN procedures are needed. The most important ongoing trials assessing effects of RDN in patients with FA are presented in Table III.

Conclusions

The second-generation trials, especially SPYRAL HTN-OFF MED Pivotal study, proved the efficacy of RDN. Achieved BP reductions were maybe slightly lower than anticipated, but were statistically significant and clinically relevant. Comparing these data with antihypertensive drug trials, this magnitude of blood pressure decrease should translate into a significantly lower risk for cardiovascular events. So it potentially justifies new recommendations for the use of RDN in clinical practice in appropriately selected patients in the new hypertension guidelines. Moreover, further data from the RADIANCE-HTN TRIO trial, in which the enrollment phase has been just completed, are upcoming and may augment the present data.

In addition, autonomic modulation by RDN has been proven, not only to reduce BP, but also to exhibit beneficial antiarrhythmic effects in patients with symptomatic AF when combined with PVI. In so far conducted randomized trials RDN was associated with significantly reduced recurrence rates of AF after PVI in hypertensive patients and may be used in this indication.

Table II. Baseline characteristics and results of prospective, randomized trials assessing the effects of renal denervation in addition to pulmonary vein isolation in patients with atrial fibrillation

Study	Patients characteristics	No. of pts in PVI with RDN/ PVI alone group	Primary outcome	ETHODS		Follow-up [months]	ESULTS	
				PVI	RDN		Recurrence of AF in PVI with RDN/PVI alone group	Effects on blood pressure (change in office SBP) in PVI with RDN/ PVI alone group
Pokushalov *et al.* (2012)	Age: 57 ±9 years Resistant HTN PAF 33%	13/14	Freedom from AF (4 × Holter monitoring at 3, 6, 9, 12 months)	RF + CTI ablation in pts with AFl	Thermocool *n* = 13	12	30.8%/71.4%	–25 mm Hg/–5 mm Hg
Pokushalov *et al.* (2014)	Age: 56 ±6 years Resistant HTN PAF 44%	41/39	Freedom from AF (4 × H olter monitoring at 3, 6, 9, 12 months)	RF + CTI ablation in pts with AFl	Thermocool *n* = 20 Symplicity *n* = 11	12	36.6%/58.9%	–21 mm Hg/–2 mm Hg
Romanov *et al.* (2016)	Age: 56 ±6 years Resistant HTN PAF 41%	39/37	Freedom from AF (implantable cardiac monitor)	RF	Thermocool *n* = 28 Symplicity *n* = 11	12	36.9%/59.5%	NA
Kiuchi *et al.* (2017)	Age: 60 ±15 years Controlled HTN PAF 100%	39/96	Freedom from AF (4 × H olter monitoring at 3, 6, 9, 12 months)	RF	Therapy cool path *n* = 39	22	38.5%/61.5%	–3 mm Hg/+1 mm Hg
Kiuchi *et al.* (2018)	Age: 58 ±6 years Resistant HTN PAF 100% Pacemaker	33/36	Freedom from AF (pacemaker)	RF	EnligHTN *n* = 33	12	39.4%/63.9%	–19 mm Hg/–10 mm Hg
Steinberg *et al.* (2020)	Age: 60 ±7 years Uncontrolled HTN PAF 100%	154/148	Freedom from AF AF burden (4 × H olter monitoring at 3, 6, 9, 12 months)	Cryoablation + CTI ablation in pts with AFl	Irrigated EP *n* = 148 RDN cath *n* = 6	12	37.0%/53.4%	–17 mm Hg/–2 mm Hg
Meta-analysis Ukena *et al.* (2020)	Age: 57.8 ±8.2 years HTN on 3 ±0.6 drugs PAF 84%	319/370	Freedom from AF	– 387 pts RF ablation – 302 pts cryoablation additionally in 95 pts CTI ablation	– 249 pts cardiac ablation catheters – 70 pts designed, nonirrigated RF catheter system	12	36.9%/58.4% OR for recurrence of AF for PVI with RDN vs. PVI alone 0.43 (95% CI: 0.32–0.59)	–17 mm Hg/–4 mm Hg

AF – atrial fibrillation, EP – electrophysiological, HTN – hypertension, PAF – paroxysmal atrial fibrillation, PVI – pulmonary vein isolation, RDN – renal denervation, RF – radiofrequency ablation, SBP – systolic blood pressure.

Table III. Ongoing prospective, randomized trials assessing the effects of renal denervation in patients with atrial fibrillation

Trial	Design	Status	Location	Enrollment	Intervention	Outcome	Start	Estimated completion date
ERDAF study (Effect of Renal Denervation on Atrial Fibrillation) *NCT04055285*	Prospective Randomized Open label	Not recruiting yet	Greece	30 participants with resistant HTN and paroxysmal or persistent AF	RDN and ILR implantation vs. optimal antihypertensive treatment and ILR implantation	Recurrence of AF and AF burden (with the use of ILR)	January 2020	December 2022
Ultrasound-Based Renal Sympathetic Denervation as Adjunctive Upstream Therapy During Atrial Fibrillation Ablation (ULTRA-HFIB) *NCT04182620*	Prospective Randomized Single-blinded	Recruiting	USA	130 participants with uncontrolled hypertension and paroxysmal or persistent AF	RDN and catheter ablation vs. catheter ablation only	Recurrence of AF up to 12 months	July 2020	December 2021
Treatment of Atrial Fibrillation in Patients by Pulmonary Vein Isolation in Combination With Renal Denervation or Pulmonary Vein Isolation Only (ASAF) *NCT 02115100*	Prospective Randomized Open label	Recruiting	Netherlands	138 participants with resistant hypertension and AF	RDN and PVI vs. PVI only	Recurrence of AF	March 2014	December 2020
Renal Nerve Denervation in Patients With Hypertension and Paroxysmal and Persistent Atrial Fibrillation (Symplicity AF) *NCT02064764*	Prospective Randomized, Open label	Active, not recruiting First results in 2020	USA	245-participants with uncontrolled HTN and AF	RDN and PVI (cryoablation) vs. PVI (cryoablation) only	Recurrence of AF	February 2015	September 2020

AF – atrial fibrillation, HTN – hypertension, PVI – pulmonary vein isolation, RDN – renal denervation.

Conflict of interest

The authors declare no conflict of interest.

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