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Review Article

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Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension: A Meta-Analysis

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Abstract

Background: Hypertension is a major risk factor to coronary artery disease and stroke being its control a cornerstone on primary and secondary prevention. Catheter ablation of the renal sympathetic innervations is a new and promising therapy but data is still limited. We aimed to evaluate its effectiveness in a meta-analysis of the available clinical trials.

Methods: We searched PubMed, EMBASE, and Cochrane databases from 1966 through July 2012. The studied outcomes were 10% or higher reduction in blood pressure and reduction in the number of needed anti-hypertensive agents. We also evaluated renal function and procedure related complications. We performed fixed effect analysis when I^2 up to 40% and P at least 0.10, otherwise we used random effect.

Results: Out of 396 articles four articles presented the studied data and were included in the analysis. The pooled data provided a total of 177 patients, being 107 submitted to denervation and 70 controls. Patients submitted to renal denervation had when compared to control a 12 fold increase in the odds of having at least 10% blood pressure reduction and a 4 fold increase in the odds of being on 3 or less anti-hypertensive after six to twelve months, p<0.01 and p=0.02 respectively. Their decrease in systolic and diastolic pressures ranged in-between 22 and 32 and 10 and 12 mmHg respectively as compared to controls. There was no deterioration in renal function. There was a 1.1% complication rate including 3 pseudoaneurysm and 1 renal artery dissection, none of them lethal.

Conclusion: Catheter-based renal seems to be a safe and efficacious adjuvant therapy for resistant hypertension.

Keywords

Hypertension; Denervation; Catheter ablation

Introduction

One in each 3 US residents has hypertension [1], and approximately 8% of US adult population has undiagnosed hypertension [2], with more than 76 million diagnosed with the disease [3]. The prevalence of hypertension has been increasing among US population, and it is estimated that by 2030, additional 27 million people will have high blood pressure, a 9.9% increase from 2010 [4]. Along the years, there were a lot of improvement on the diagnosis and treatment of hypertension. National Health and Nutrition Examination Survey (NHANES) has compared the period of 1988-1994 and 2007-2008 and has found that the blood pressure control has risen from 27.3% to 50.1%, respectively, and the treatment enrollment has increased from 50.6% to 73.5% [5]. The control/treatment ratio has changed from 50.6% to 72.3% [6]. Despite substantial progress in the diagnosis and treatment of hypertension, around 8.9% of the hypertensive population, close to 9 million people, even being treated with at least three antihypertensive drugs, remains with elevated arterial blood pressure [7], which defines resistant hypertension [8]. Therefore, the adequate blood-pressure control to ideal target values remains suboptimal.

The renal sympathetic nervous system plays one of the major physiological mechanisms for hypertension. It controls both peripheral and central regulation of blood pressure. The afferent sympathetic renal system acts on the central control activation for increasing the cardiac output and the peripheral arterial resistance [9,10]. Renal sympathetic system is an important contributing factor for resistant hypertension. Surgical sympathetic denervation has been shown to be an effective means of reducing sympathetic outflow to the kidneys, augmenting natriuresis and diuresis, and reducing renin release, without adversely affecting other functions of the kidney such as glomerular filtration rate and renal blood flow [11,12].

Renal artery ablation is a technique based on the percutaneous access via the lumen of the renal artery, and four to six low-power radiofrequency ablations are deployed throughout the artery wall. The procedure has been shown to be safe and feasible in Europe [13,14]. Nevertheless, complications regarding the procedure have had low incidence of immediate periprocedural complications and short- and medium-term renal and vascular complications (at 6-12 months). There was less than 5% overall reported procedure complications mainly described as renal artery dissection or femoral pseudoaneurysms [15-19].

In this review, we present a meta-analysis of controlled trials in the published literature evaluating effectiveness and safety of catheter-based renal ablation for reduction of blood pressure and anti-hypertensive drugs in patients with resistant hypertension.

Methods

Search strategy

We systematically searched PubMed, EMBASE, and Cochrane Central Register of Controlled Trials for clinical studies with treatment groups participants to renal denervation versus a comparator for resistant hypertension from 1966 through July 2012. The following medical subject heading terms were included for a MEDLINE search and adapted for other databases as needed: “renal denervation,” “sympathetic renal denervation,” “resistant hypertension,” “refractory hypertension,” and “elevated blood pressure”. In addition to searching databases, reference lists of all included studies, meta-analyses, and reviews were manually searched.

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There was no language restriction for the search. We included trials that studied adult (18-year-old) patients and reported relevant clinical outcomes with renal denervation. Eligible studies had to be clinical prospective studies comparing renal denervation to comparators and have reported the outcomes of interest. We included all clinical studies with renal denervation for resistant hypertension because our objective was to study hypertension outcomes with renal denervation in a wide variety of populations. We excluded trials of patients where renal denervation was used as an adjunct, those in which renal denervation was also used in the control group, case series, and those that did not report the outcomes of interest.

Data extraction

Data extraction and quality assessment were independently completed by two authors (FYM and AB) and in duplicate reporting to the coordinator (DG) who reviewed the trials to ensure that they met the inclusion criteria and abstracted the data. Disagreements were resolved by consensus (10% of the time) and by the senior author of the study (EDM).

Selection criteria

We performed objective assessment of trials using the method specified in the Cochrane Handbook of Systematic Reviews assessing for randomization, concealment, blinding, intention to treat, baseline comparisons, concomitant interventions, and completeness of follow-up. Our primary outcome was those patients who presented with sustained reduction of systolic blood pressure greater than 10 mmHg for the follow-up period of the trial. Maximum duration of follow-up assessed for the study was 24 months. Secondary outcomes of interest were patients who decreased the number of antihypertensive agents, post-procedure complication and procedure safety.

Statistical analysis

Meta-analysis was performed according to recommendations of the Cochrane Collaboration and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Pooled treatment effects were estimated using risk ratio (RR) with the Mantel–Haenszel risk ratio in a random-effects model. Heterogeneity was assessed using chi-square tests and I2 statistic; we defined I^2 <25% as low heterogeneity according to the Cochrane Handbook of Systematic Reviews. We assessed quality for each included trial; all included trials were controlled trials and were considered high quality. For statistical analysis, we used Review Manager 5.1 (Nordic Cochrane Centre, Cochrane Collaboration, and Copenhagen, Denmark) and STATA 11 (STATA Corp., College Station, Texas).

Results

Study selection. Our MEDLINE search yielded 374 studies. After elimination of duplicate results, the EMBASE and Cochrane registries did not yield additional studies. Through a review of titles and abstracts, 365 studies were rejected for lack of relevance. The remaining nine articles were reviewed and assessed for satisfaction

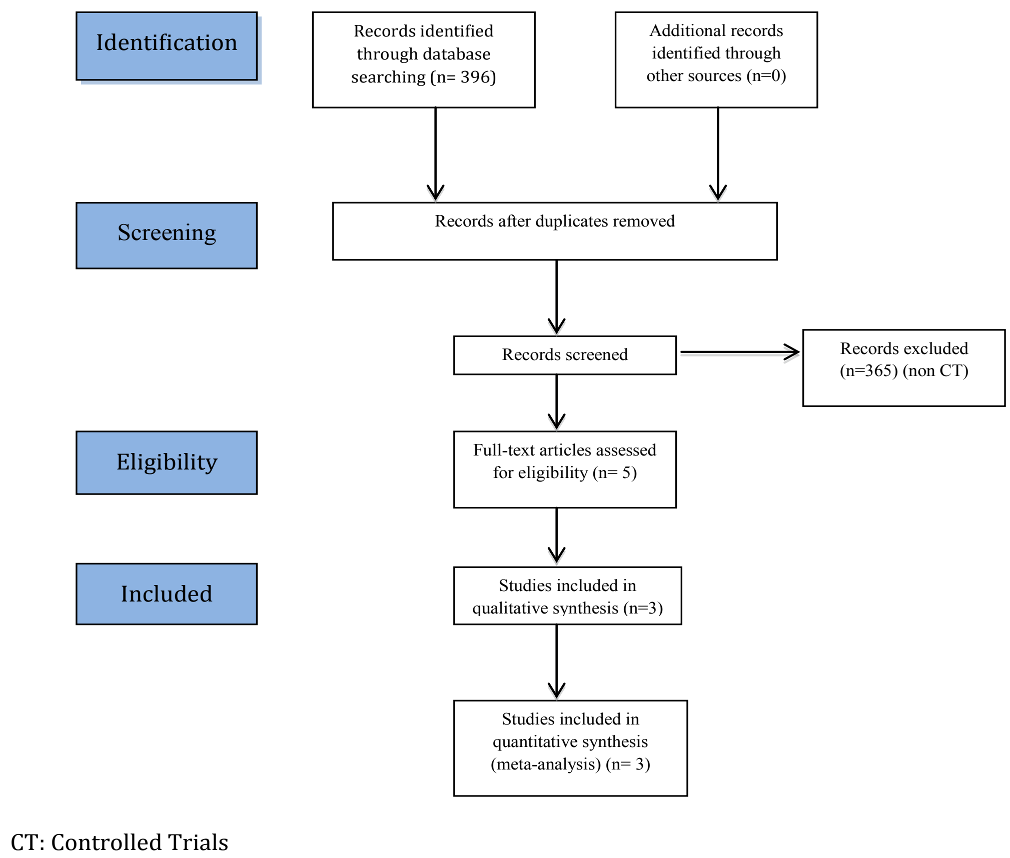

Figure 1: Study Selection Design.

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Table 1: Baseline Characteristics of the Studies.

Trial	Population	Intervention Group	Control Group	BP Measure	MedicationCompliance	Follow up
Symplicity HTN2	106	52	54	24H ABPM Home-based Office-based	Daily note of drug intake for 2 weeks	1, 3 and 6 mo
Pokushalov et al. [17]	24	13	14	Office-based BP	Ask directly to the patient at the office	3,6,9,12 mo
Krum et al. [19]	50	45	5	Office-based BP	Ask directly to the patient at the office	1, 3, 6, 12 mo

- Incluson Criteria was the same for all trials: Patients aged 18–85 years with a systolic blood pressure of 160 mm Hg or more (150 mm Hg in patients with type 2 diabetes), despite compliance with three or more antihypertensive drugs.
- Exclusion criteria was the same for all trials: an estimated glomerular filtration rate (eGFR; based on the Modification of Diet in Renal Disease criteria12) of less than 45 mL/min per 1·73 m, type 1 diabetes, contraindications to MRI, substantial stenotic valvular heart disease, implanted pacemakers or defibrillators, pregnancy or planned pregnancy during the study, and a history of myocardial infarction, unstable angina, or cerebrovascular accident in the previous 6 month, with hemodynamically significant renal artery stenosis, previous renal artery intervention, or renal artery anatomy that precluded treatment (defined as <4 mm diameter, <20 mm length, or more than one main renal arteries).
- Renal artery ablation technique was the same used in all trials: Up to 6 ablations at 8 Watts for 2 min each were performed in both renal arteries.
- 24Hours Ambulatory Blood Pressure Measure (24H ABPM):15 minutes in daytime and 30 minutes in night-time, and calculated overall 24H changes (according to European Society of Cardiology and European Society of Hypertension guidelines).
- Home-based blood pressure (BP): measured 2 weeks before follow up appointment.

of the inclusion or exclusion criteria. The four articles that met all criteria were included in this analysis (Figure 1 and Table 1).

Baseline characteristics

The pooled data provided a total of 244 patient and those 156 and 88 patients were enrolled in the renal denervation and control groups, respectively, with a mean age of 59 years and men being 56%. Patients were treated after a renal denervation protocol that was similar for all the studies included in this meta-analysis with up to 6 ablations at 8 W for 2 min each in both renal arteries [14], and BP was measured as presented in Table 2. In all studies, patients were evaluated at the first month post-procedure except for Pokushalov et al. [16]. Brandt et al. [16] evaluated the patients at 6 months, and in all other trials, patients were seen at 3 months as well. Krum et al. [19] and Pokushalov et al. [17] were the only studies to perform 1-year follow-up. All patients were recommended to continue on the same antihypertensive regimen in all studies analyzed; adjustment on the regimen was applied according to the blood pressure variation on the follow up visits.

Efficacy and blood pressure reduction

All the studies reported the mean, standard deviation and for systolic and diastolic blood pressure at baseline and Pokushalov et al. also reported p value (Table 2). The absolute significant reduction on systolic and diastolic blood pressure was present on the intervention group up to 6 months follow-up (p<0.05) (Figure 2). As demonstrated in Figure 3, patients submitted to renal denervation had when compared to control a 12 fold increase in the odds of having at least 10% systolic blood pressure reduction (p<0.05). Pokushalov et al. and Krum et al. mentioned a significant systolic and diastolic blood pressure reduction greater than 20/10 mmHg respectively sustained up to 12 months.

Antihypertensive medication withdrawn

The reduction of patients taking three or more antihypertensive medication was frequently seen in the groups treated with renal denervation (Figure 3). Pokushalov et al. showed the most significant reduction was by 25% followed by Symplicity HTN-2 with 20% reduction and Krum et al with 10%. When all data were analyzed together, the renal denervation favors the medication number reduction with a 4 fold increase in the odds of being on 3 or less anti-hypertensive medication after six months (p<0.05), another positive secondary benefit of the procedure. In further analyzing the data, some studies reported medication dose reduction, but it was not studied in all trials either the initial proposal of our analysis.

Post-procedure complication

There was one case of pseudo aneurysm at the femoral access site present in each study except for Brandt et al. [16], who did not show any. Krum et al. [19] reported the only case of renal artery dissection. There was no renal function deterioration in any study.

Discussion

Our study is able to expand previous reports on blood pressure control in patients with resistant hypertension. We could show that treatment with catheter-based renal denervation across a wide spectrum of patients with uncontrolled essential hypertension despite medical treatment with three or more antihypertensive drugs resulted in a trend toward a sustained reduction of systolic and diastolic blood pressure over time. Also, the study demonstrated that this new technique is safe and tends to reduce the number of antihypertensive medication. None of the studies showed any significant post-procedure complication neither renal function deterioration.

We can say that physiological benefits of suppression of the renal autonomic sympathetic system can be beneficial for reasons other than those previously pointed and extrapolated for other medical conditions. It can be used in those conditions were sympathetic activation is a component of the underlying disease process and leads to increased sodium and in body fluid retention. Congestive heart failure [16], obstructive sleep apnea [18], and hypertension accompanying end-stage renal disease [20] are some of the conditions that renal ablation may be beneficial. Nevertheless, there are some other pleiotropic effects of renal denervation that provides indirect improvements by blood pressure modification. It has been shown that renal denervation and blood pressure control can significantly reduce the left ventricle mass, with consequent improvement upon diastolic ventricular function [16]. Also, it has been demonstrated that renal denervation can improve not only blood pressure control but also insulin resistance and glucose metabolism [21].

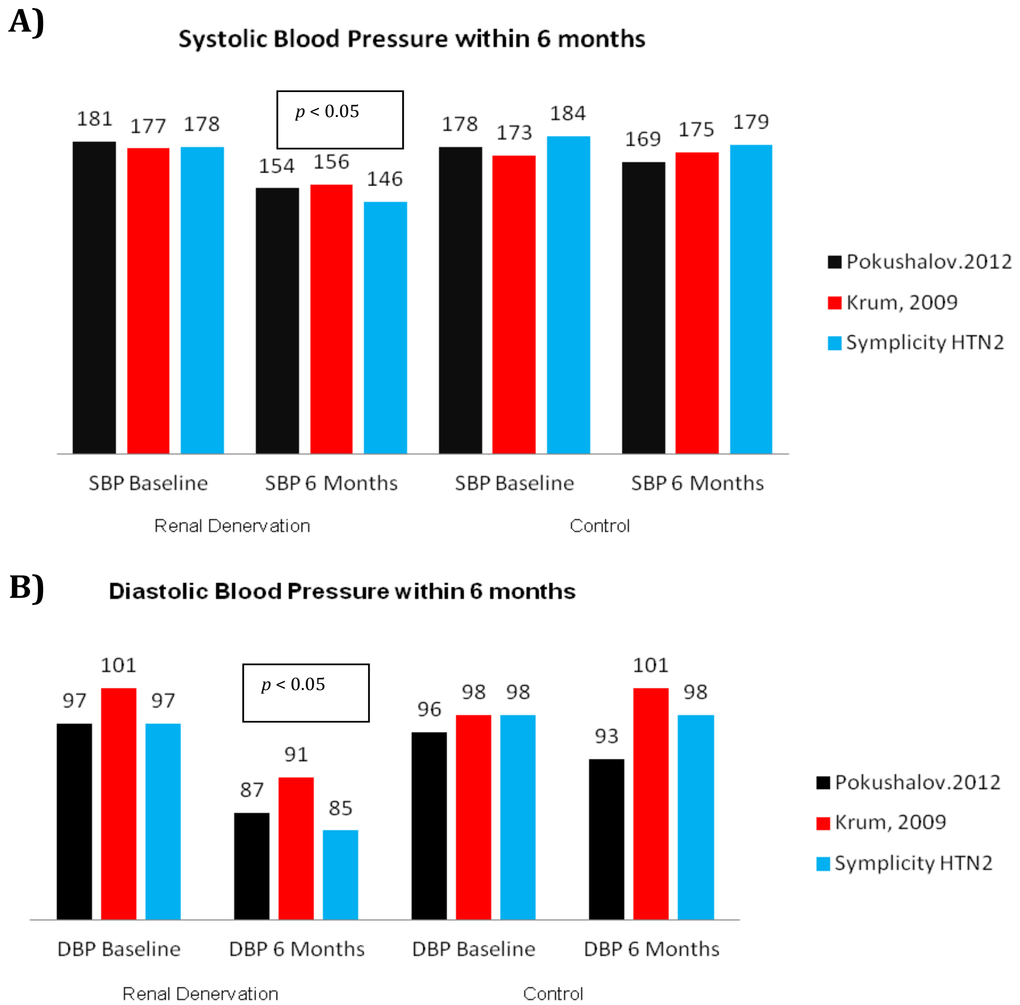
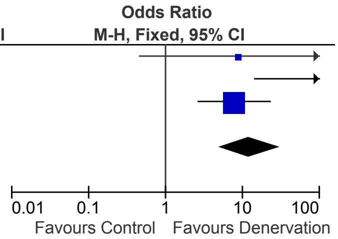


Figure 2: Systolic and Diastolic Absolute and Relative Blood Pressure Reduction.

A)

Study or Subgroup	Renal Denervation Events	Renal Denervation Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Krum 2009	20	45	0	5	15.3%	8.84 [0.46, 169.44]
Pokushalov 2012	13	13	0	14	0.5%	783.00 [14.49, 42299.61]
Symplicity HTN2	44	49	27	51	84.2%	7.82 [2.67, 22.94]
Total (95% CI)		**107**		**70**	**100.0%**	**12.14 [4.85, 30.41]**
Total events	77		27			

Heterogeneity: Chi² = 4.88, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 5.33 (P < 0.00001)



B)

Study or Subgroup	Renal Denervation Events	Renal Denervation Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Krum 2009	4	45	0	5	22.8%	1.19 [0.06, 25.29]
Pokushalov 2012	3	13	0	14	10.3%	9.67 [0.45, 207.78]
Symplicity HTN2	10	49	3	51	66.9%	4.10 [1.06, 15.95]
Total (95% CI)		**107**		**70**	**100.0%**	**4.01 [1.27, 12.67]**
Total events	17		3			

Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)

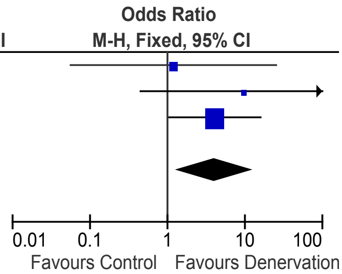


Figure 3: Systolic and Anti-Hypertensive Drug Reduction. **A)** Chance of Having Reduction of 10% or Greater on Systolic Blood Pressure. **B)** Chance of Being on 3 or Less Anti-Hypertensive Drugs.

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Table 2: Baseline Characteristics of Subjects.

	Symplicity HTN2			Pokushalov et al. 2012			Krum et al. 2009		
	Intervention	Control	*p* value	Intervention	Control	*p* value	Intervention	Control	*p* value
Age	58 ± 12	58 ± 12	-	57 ± 8	56 ± 9	0.41	58 ± 9	51 ± 8	--
Sex (Female)	18 (35%)	27 (50%)	-	4 (30%)	4 (28%)	0.47	20 (44%)	1 (20%)	-
BMI	31 ± 5	31 ± 5	-	28 ± 5	28 ± 6	0.83	-	-	-
Systolic BP	178 ± 18	178 ± 16	-	181±7	178 ± 8	0.61	177 ± 20	173 ± 8	-
Diastolic BP	97 ± 16	98 ± 17	-	97 ± 6	96 ± 4	0.58	101 ± 15	98 ± 9	-
Number Anti-Hypertension Medication	5.2 ± 1.5	5.3 ± 1.8	-	3.8 ± 0.4	3.6 ± 0.6	-	4.7 ± 1.5	4.6 ± 0.5	-
GFR	77 ± 19	86 ± 20	-	78 ± 6.1	80.2 ± 4.6	0.46	87 ± 23	95±15	-
Heart Rate	75 ± 15	71 ± 15	-	-	-	-	72 ± 11	79 ± 9	-
Creatinine	0.91 ± 0.25	0.78 ± 0.18	-	-	-	-	-	-	-
DSLD	27 (52%)	28 (52%)	-	3 (23%)	3 (21%)	0.62	29 (64%)	5 (100%)	-
CAD	10 (19%)	4 (7%)	-	2 (15.3%)	2 (14.2%)	0.32	10 (22%)	1 (20%)	-
DM	21 (40%)	15 (28%)	-	1 (7.7%)	2 (14.2%)	0.32	14 (31%)	2 (40%)	-
ACE inhibitors/ARB	50 (96%)	51 (94%)	-	12 (92%)	14 (100%)	0.78	43 (96%)	4 (80%)	-
Direct renin inhibitor	8 (15%)	10 (19%)	-	-	-	-	34 (76%)	51 (100%)	-
Beta blocker	43 (83%)	37 (69%)	-	10 (78%)	10 (71%)	0.61	31 (69%)	51 (100%)	-
Calcium channel blocker	41 (79%)	45 (83%)	-	10 (78%)	10 (71%)	0.61	-	-	-
Diuretics	46 (89%)	49% (91%)	-	13 (100%)	13 (92%)	0.73	43 (96%)	3 (60%)	-

(-): information not available, BP: Blood Pressure, BMI: Body mass index; The body-mass index is the weight in kilograms divided by the square of the height in meters, GFR: glomerular filtration rate; DSLD: dislipidemia; CAD: coronay artery disease; DM: diabetes mellitus, ACE: angiotensin- converting enzyme, ARB: angiotensin-receptor blocker.

Pokushalov et al. [17] was able to study patients with associated atrial fibrillation and resistant hypertension. They all underwent pulmonary vein ablation as therapy for atrial fibrillation and then randomized to renal artery ablation. It was concluded that renal artery ablation has not only influenced on resistant hypertension control but also on the recurrence of atrial fibrillation.

This analysis presents some limitations regarding the small number of patients enrolled and lack of randomization in some of them. There were four studies eligible for analysis and they counted in total for only 244 patients in total what could have narrowed the interval for statistical significant differences. On the other hand, it could have strengthened the significant findings for sustained blood pressure control. Nevertheless, there is a also a lack of sham procedure on the control group. The following simplicity HTN-3 [22] that has been just started in the USA will address this and will perform the renal catheterization in all the patients and later patients will be sedated and randomly assigned to ablation.

Catheter-based renal artery ablation indirectly acts against the renin angiotensin system. In prospective studies, the prevalence of primary hyperaldosteronism has ranged from 14% to 21% [23,24] in patients with resistant hypertension, which is considerably higher than that in the general hypertensive population. Furthermore, marked antihypertensive effects are seen when mineralocorticoids antagonists are added or compared with the other antihypertensive agents to the treatment regimen of patients with resistant hypertension [25-28]. This can be a good evidence that therapies, such as aldosterone excess, is an important cause for resistance, and its suppression is a good therapy approach. Nevertheless, we could seek that combined therapy with renal ablation and spironolactone, an aldosterone antagonist can cause a more pronounced benefit on resistant hypertension treatment.

The analysis suggests that catheter-based renal ablation tends to be a safe technique and beneficial for resistant hypertension management when other therapies have failed. This approach is sustained by the idea that denervation of efferent renal sympathetic fibers can reduce the renal noradrenalin spillover [13], and the ablation of afferent renal nervous system can reduce the whole-body sympathetic activation that stimulates the sympathetic outflow from the hypothalamus [13,26].

In conclusion, the sustained blood pressure control and the decrease in number of antihypertensive medication shown on the analysis support the idea of previous studies of sustained blood pressure and antihypertensive medication reduction. Catheter-based renal artery ablation approach is a recent technique that has just been initiated and this analysis gives a strong support to continue large clinical trials.

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